From: Susan Hintz
To: Kathy J Auten
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT MRI STUDY
Date: Sunday, December 31, 2006 7:42:24 PM

Thanks so much Kathy!

Susan

Kathy J. Auten, MSHS
Project Manager
NICHD Neonatal Research Network Trials
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

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

12/15/2006 11:22

To

<goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Kathy J Auten" <auten002@mc.duke.edu>

cc

"Susan Hintz" <srhintz@stanford.edu>, "Neil Finer" <nfiner@ucsd.edu>

bcc

Subject

SUPPORT MRI STUDY

HI - A couple things for the SUPPORT MRI Study -

-

Please respond to the following questions by **DECEMBER 30TH, 2006**

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 2

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 1

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:

a) How many died before reaching the 35-42 week window? 0

b) How many have not yet reached the window? 0

c) How many have reached the window, but have not yet been imaged? 1

d) How many "missed"/were unsuccessful with a neuroimaging study?

Please describe: _____infant unstable, have been told we may schedule MRI for this coming week

e) Other issues? 2 other candidates died prior to enrollment
Please describe: _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? _1___

Late cranial US? _1___

Brain MRI? 1

****Thank you**for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!****

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, MD20892

(For overnight delivery, use Rockville, MD20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From:	Kathy J Auten
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	srhintz@stanford.edu; nfiner@ucsd.edu; cotte010@mc.duke.edu; goldb007@mc.duke.edu
Subject:	Re: SUPPORT MRI STUDY
Date:	Sunday, December 31, 2006 9:31:35 AM

Kathy J. Auten, MSHS
Project Manager
NICHD Neonatal Research Network Trials
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

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

12/15/2006 11:22

To <goldb008@mc.duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Kathy J Auten" <auten002@mc.duke.edu>

cc "Susan Hintz" <srhintz@stanford.edu>, "Neil Finer" <nfiner@ucsd.edu>

bcc

Subject SUPPORT MRI STUDY

HI – A couple things for the SUPPORT MRI Study -

-

Please respond to the following questions by **DECEMBER 30TH, 2006**

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 2

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 1

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:

a) How many died before reaching the 35-42 week window? 0

b) How many have not yet reached the window? 0

c) How many have reached the window, but have not yet been imaged? 1

d) How many "missed"/were unsuccessful with a neuroimaging study?

Please describe: _____infant unstable, have been told we may schedule MRI for this coming week

e) Other issues? 2 other candidates died prior to enrollment
Please describe: _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? _1___

Late cranial US? _1___

Brain MRI? 1

****Thank you**for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!****

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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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Mcdavid, Georgia E
To: Higgins, Rosemary (NIH/NICHD) [E]; Tyson, Jon E; Morris, Brenda H
Cc: Susan Hintz; Neil Finer
Subject: RE: SUPPORT MRI STUDY
Date: Friday, December 22, 2006 12:35:47 PM

Here is our information as of 12/21/06

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 15, 2006 10:22 AM
To: Tyson, Jon E; Morris, Brenda H; Mcdavid, Georgia E
Cc: Susan Hintz; Neil Finer
Subject: SUPPORT MRI STUDY

HI – A couple things for the SUPPORT MRI Study -

Please respond to the following questions by **DECEMBER 30TH, 2006**

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 27

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 12

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:

a) How many died before reaching the 35-42 week window? 6
b) How many have not yet reached the window? 7
c) How many have reached the window, but have not yet been imaged? 1
d) How many "missed"/were unsuccessful with a neuroimaging study? 1
Please describe: MRI done- HUS requested but was missed prior to discharge
e) Other issues?
Please describe: _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? none
Late cranial US? none
Brain MRI? none

****Thank you** for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!**

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: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Nancy.Miller@UTSouthwestern.edu
Subject: Re: Fw: SUPPORT MRI
Date: Monday, December 18, 2006 4:35:26 PM

Hi Nancy,

Thanks very much for the information. Do you guys have the MedVac immobilizer? Do you feel that the movement issues are better or were those 2 patients recent?

Are you and your radiologists feeling good about the MRI images? If you have any concerns, I can make sure the Pat Barnes looks at the images as soon as RTI gets them -

Thanks so much for your hard work on this secondary!

Susan

>----------
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
>From: Nancy Miller <Nancy.Miller@UTSouthwestern.edu>
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Gaynelle Hensley <Gaynelle.Hensley@UTSouthwestern.edu>; Pablo
>Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Walid Salhab
><Walid.Salhab@UTSouthwestern.edu>
>Sent: Mon Dec 18 15:49:28 2006
>Subject: Re: SUPPORT MRI
>
>
>Rose,
>We have enrolled 8 patients in the SUPPORT Neuroimaging secondary and
>all 8 have had the HUSs and MRIs done. One patient required two attempts
>for the MRI due to movement. Three MRIs have been copied but haven't
>been sent. I just sent a request to CMC for the other 5 MRIs to be
>copied. I would like to send the HUSs and MRIs together and we will be
>learning how to copy the HUSs to CDs tomorrow. I'll send the copies to
>RTI as soon as we have all of these done.
>Thanks,
>Nancy
>
>
>Nancy A. Miller, R.N.
>Department of Pediatrics
>Division of Neonatal-Perinatal Medicine
>UT Southwestern Medical Center at Dallas
>5323 Harry Hines Blvd. E3-502
>Dallas, Texas 75390-9063
>214-648-3780
>pager 972-206(b) (6)
>

>>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>12/15/2006 10:20 AM >>>
>HI - A couple things for the SUPPORT MRI Study -
>
>
>
>Please respond to the following questions by DECEMBER 30TH, 2006
>
>
>
>1) How many patients have been enrolled to date in the SUPPORT
>Neuroimaging secondary at your site?
>
>
>
>2) How many have completed 35-42 week neuroimaging studies (MRI and
>CUS)
>
>
>
>3) If you have enrolled patients that have not completed 35-42 week
>neuroimaging, please tell us:
>
> a) How many died before reaching the 35-42 week window?
>
>b) How many have not yet reached the window?
>
> c) How many have reached the window, but have not yet been
>imaged?
>
> d) How many "missed"/were unsuccessful with a neuroimaging
>study?
>
>Please describe: _____
>
>e) Other issues?
>
>Please describe: _____
>
>
>
>4) How many of the following neuroimaging studies have been copied and
>sent to RTI?
>
> Early cranial US? _____
>
> Late cranial US? _____
>
> Brain MRI? _____
>
>
>
>**Thank you for your hard work and dedication on SUPPORT and the
>Neuroimaging Secondary!**
>
>
>

>
>
>
>
>
>
>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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>(For overnight delivery, use Rockville, MD 20852)
>
>301-435-7909
>
>301-496-3790 (FAX)
>
>higginsr@mail.nih.gov
>
>

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: wrich@ucsd.edu
Subject: Re: Fw: support mri
Date: Monday, December 18, 2006 4:25:26 PM

Hi Wade,

Strange, because I have down that you already have 12 patients with 12 having completed neuroimaging at 35-42 weeks. That was an update from June...Are you reporting below just the patients since you have re-started enrollment?

Let me know

Susan

>----------
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
>From: Wade Rich <wrich@ucsd.edu>
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Sent: Mon Dec 18 10:24:13 2006
>Subject: RE: support mri
>
>Center 22
>
> 1) How many patients have been enrolled to date in the SUPPORT
>Neuroimaging secondary at your site? 10
>
>
>
>2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 8
>
>
>
>3) If you have enrolled patients that have not completed 35-42 week
>neuroimaging, please tell us:
>
> a) How many died before reaching the 35-42 week window? 0
>
> b) How many have not yet reached the window? 0
>
> c) How many have reached the window, but have not yet
>been imaged? 2
>
> d) How many "missed"/were unsuccessful with a neuroimaging study?
>
>Please describe: _ No unsuccessful studies _____
>
>e) Other issu
>
>Please describe: ___ 2 discharged before a study could be arranged. _____

>
>
>
>4) How many of the following neuroimaging studies have been copied
>and sent to RTI?
>
> Early cranial US? ___ 10 _____
>
> Late cranial US? ____ 10 ___
>
> Brain MRI? ____ 8 _____

From:	Zaterka-Baxter, Kristin
To:	Gordon Avery; rjb6j@hscmail.mcc.virginia.edu; cgleason@u.washington.edu; Willinger, Marian (NIH/NICHD) [E]; Clemons, Traci (NIH/NICHD); mikeross@ucla.edu; kant@unc.edu; merran.thomson@ic.ac.uk; Marilee Allen; GailD@nih.gov; Das, Abhik; Gantz, Marie
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Huitema, Carolyn Petrie; Monica Bocaner; Webb, Robin E.
Subject:	NICHD NRN DSMC Support Study Mtg (02/16/07)
Date:	Monday, December 18, 2006 12:20:38 PM
Attachments:	DSMCMembersList20061213.doc Support DSMC Memo20070206.doc

Dear DSMC members,
The meeting date for the first planned DSMC review of the NICHD NRN study titled "The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)" has been scheduled for Tuesday February 6, 2007 in Rockville, MD. Please find attached the DSMC roster and logistics memo including contacts should you have any questions regarding the meeting. Approximately one week prior to the meeting date, we will be sending out study reports to be reviewed during the meeting. We will have a conference line set up for those who will be joining us by phone. Instructions for the call will be sent closer to the meeting date.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

NICHD Neonatal Research Network DSMC Membership Roster 12/13/06

Gordon Avery, MD ***(DSMC Chair)***
Specialty: Neonatology, Clinical Trials
Telephone: (703) 820-3134
Cell: (703) 405(b)
e-mail(b) (6)

Robert J. Boyle, MD
Specialty: Neonatology, Bioethics
Professor of Pediatrics
Dept. of Pediatrics,
Division of neonatology
Room 3747, Old Medical School
Hospital Drive
University of Virginia Health System
Charlottesville, VA 22908-0386
Telephone: (434) 924-5429
Fax: (434) 924-2816
e-mail: RJB6J@hscmail.mcc.virginia.edu

Christine A. Gleason, MD
Specialty: Neonatology, Cerebral-vascular Physiology
Department of Pediatrics
University of Washington
1959 NE Pacific St., HSB RR451
Seattle, WA 98195
Telephone: (206) 543-3200
Fax: (206) 543-8926
e-mail: cgleason@u.washington.edu

Marian Willinger, PhD
Specialty: Control of Breathing, SIDS
Pregnancy and Perinatology Branch,
Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
6100 Executive Blvd, 4B03
Bethesda, MD 20892
Telephone: (301) 435-6896
Fax: (301) 496-3790
e-mail: willingm@mail.nih.gov

Traci Clemons, Ph.D.
Specialty: Biostatistics and Clinical Trials
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850
Telephone: (301) 251-1161x212
Fax: (301) 251-1355
e-mail: tclemons@emmes.com

Michael G. Ross, M.D., M.P.H.
Specialty: High-risk pregnancy and maternal-fetal medicine.
Professor of Ob/Gyn and Public Health, UCLA School of Medicine and Public Health; Chairman, Department of Ob/Gyn.
Harbor-UCLA Medical Center
1000 W. Carson Street, Box 3
Torrance CA 90509
On-campus mail: 176847
Tel: (310) 222-3544
Fax:(310) 782-8148
E-mail: mikeross@ucla.edu

Shrikant Bangdiwala , PhD
Specialty: Biostatistics
Research Professor Biostatistics
School of Public Health
Suite 203, Bank of America Center
University of North Carolina at Chapel Hill
137 E. Franklin Street
Chapel Hill, North Carolina 27514-4145
Phone: 919-962-3266
Fax: 919-962-3265
Email: kant@unc.edu

NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

Merran A. Thomson, MD
Specialty: Neonatology, Respiratory Physiology
Department of Paediatrics and Neonatal Medicine
Hammersmith Hospital,
Du Cane Road
London W12 0HS (UK)
Telephone: +44 208 383 3270,
Fax: +44 208 764 8281
e-mail: merran.thomson@ic.ac.uk

Marilee C. Allen, MD
Specialty: Neonatology, High risk infant follow-up, Neurodevelopment
Associate Professor of Pediatrics
Department of Pediatrics/Division of Neonatology
The Johns Hopkins University School of Medicine
600 N. Wolfe St., CMSC 210
Baltimore MD 21287-3200
Telephone: (410) 955-4566
Fax: (410)955-0298
e-mail: mcallen@jhmi.edu

Dorothy Gail, PhD,
Specialty: Lung Biology
Director, Lung Biology and Diseases Program, Division of Lung Diseases, NHLBI
Rockledge II, Rm 10100
Bethesda, MD 20892-7952
Phone: 301-435-0222;
Fax: 301-480-3557
Email: GailD@nih.gov

SUPPORT DSMC MEETING
RTI INTERNATIONAL - ROCKVILLE OFFICE
FEBRUARY 6, 2007

DATE & LOCATION The meeting is scheduled for Tuesday, February 6, 2007, at RTI's Rockville office, located at 6110 Executive Blvd—9th Floor, Rockville, MD 20852.

SCHEDULE The meeting will begin Tuesday morning at 8:30 am. Breakfast and lunch will be provided. The meeting will conclude by 3:30 pm. The meeting agenda and support data safety and monitoring report will be sent approximately one week prior to the meeting

HOTEL Rooms have been reserved for all out of town attendees at the DoubleTree Rockville, located at 1750 Rockville Pike, Rockville, MD 20852. Upon arrival you will be asked to give a credit card for incidentals, however RTI is covering the cost of your room. Your reservation confirmation number will be e-mailed to you.

Shuttle service is not provided to RTI for the meeting. We suggest attendees meet in the lobby around 8:00 am to share cabs to RTI. It is approximately 1.5 miles.

MEALS Breakfast and lunch will be provided the day of the meeting. For out of town guests, RTI will provide reimbursement up to the allowable federal per diem for dinner on February 5 and 6, and breakfast on February 6. An expense form will be handed out at the meeting to cover meals, airfare and ground transportation. Please save your receipts!

TAXIS AND METRO The DoubleTree is located approximately forty-five minutes from Washington Reagan National Airport or Dulles International Airport. Taxis from National and Dulles Airports cost approximately $50 and from BWI, approximately $65.

Super Shuttle is available and recommend for groups traveling together. Fares are approximately $25 for the first passenger and $8 for each additional passenger. Reservations may be made online at http://www.supershuttle.com/htm/cities/dca.htm.

You may also take the Metro from Reagan National Airport to the hotel. The DoubleTree is located right on the Twinbrook stop on the Red Line. (13 stops from Gallery Place/Chinatown.) It is about a 45 minute ride to the DoubleTree from Gallery Place/Chinatown.

- Take the Yellow Line from the airport towards Mt. Vernon Square.
- Get off at the Gallery Place/Chinatown stop.
- Change to a Red Line train towards Shady Grove; get off at Twinbrook

SPECIAL NEEDS Any attendee with special needs (e.g. special diet, handicap access) should notify RTI Conference Coordinator Monica Bocaner at monica@bocaner.net by Tuesday, January 30. Vegetarian options will be provided at breakfast and lunch. If you have any food allergies, please let us know.

QUESTIONS For logistical information, contact RTI Conference Coordinator Monica Bocaner at monica@bocaner.net or 571-220-8756. For any other questions please contact Kris Zaterka-Baxter, NRN DCC coordinator at 919-485-7750 or kzaterka@rti.org.

If something unexpected arises that necessitates canceling your attendance at the meeting, please notify Kris Zaterka-Baxter; kzaterka@rti.org or 919-485-7750 immediately so we can cancel your hotel reservation.

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: support mri
Date: Monday, December 18, 2006 10:20:23 AM

Center 22

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 10

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 8

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:

a) How many died before reaching the 35-42 week window? 0
b) How many have not yet reached the window? 0
c) How many have reached the window, but have not yet been imaged? 2
d) How many "missed"/were unsuccessful with a neuroimaging study?
Please describe: _ No unsuccessful studies _____
e) Other issu
Please describe: ___ 2 discharged before a study could be arranged. _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? ___ 10 _____
Late cranial US? ____ 10 ___
Brain MRI? ____ 8 _____

From: Susan Hintz
To: Bradley.Yoder@hsc.utah.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; roger.faiix@hsc.utah.edu
Subject: Re: Fw: [SPAM] SUPPORT MRI STUDY
Date: Friday, December 15, 2006 2:54:35 PM

Thanks Brad for the prompt response. We appreciate all your hard work on this study!

Susan
Susan R. Hintz, M.D., M.S.
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

>----------
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
>From: Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Cc: roger.faiix@hsc.utah.edu <roger.faiix@hsc.utah.edu>
>Sent: Fri Dec 15 13:25:52 2006
>Subject: Re: [SPAM] SUPPORT MRI STUDY
>
>Rose:
>You should know that our Research Coordinator has changed and is now
>Karen Osborne, not Susan Tepper.
>Karen's email is karen.osborne@hsc.utah.edu
>I have answered the questions below.
>
>>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>12/15/2006 10:23:40 AM >>>
>HI - A couple things for the SUPPORT MRI Study -
>
>
>
>Please respond to the following questions by DECEMBER 30TH, 2006
>
>
>
>1) How many patients have been enrolled to date in the SUPPORT
>Neuroimaging secondary at your site?
>Ten (all of our SUPPORT babies are enrolled as part of our initial
>consent)
>
>
>2) How many have completed 35-42 week neuroimaging studies (MRI and
>CUS)
>Three

>
>
>3) If you have enrolled patients that have not completed 35-42 week
>neuroimaging, please tell us:
>
> a) How many died before reaching the 35-42 week window?
>One
>
>b) How many have not yet reached the window? Five
>
> c) How many have reached the window, but have not yet been
>imaged? One
>
> d) How many "missed"/were unsuccessful with a neuroimaging
>study? None
>
>Please describe: _____
>
>e) Other issues?
>
>Please describe: _____
>
>
>
>4) How many of the following neuroimaging studies have been copied and
>sent to RTI?
>
> Early cranial US? _____
>
> Late cranial US? _____
>
> Brain MRI? _____
>
> All have copied but I don't think we have sent any yet (Karen Osborne
>our coordinator had shoulder surgery last week & we're waiting for her
>return to send these off.)
>
>Hope this helps.
>
>Brad
>
>**Thank you for your hard work and dedication on SUPPORT and the
>Neuroimaging Secondary!**
>
>
>
>
>
>
>
>
>
>
>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: Susan Hintz
To: Johnson, Karen
Cc: Higgins, Rosemary (NIH/NICHD) [E]; edward-bell@uiowa.edu
Subject: RE: SUPPORT MRI STUDY
Date: Friday, December 15, 2006 2:52:20 PM

Thanks so much Karen! I know this is a challenging study, and I really appreciate all the hard work you guys are doing!

Susan

Susan R. Hintz, M.D., M.S.
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

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 15, 2006 10:23 AM
To: Bell, Edward; Johnson, Karen
Cc: Susan Hintz; Neil Finer
Subject: SUPPORT MRI STUDY

HI - A couple things for the SUPPORT MRI Study -

Please respond to the following questions by **DECEMBER 30TH, 2006**

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 2

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 0

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:

a) How many died before reaching the 35-42 week window? 0

b) How many have not yet reached the window? 2

c) How many have reached the window, but have not yet been imaged? 0

d) How many "missed"/were unsuccessful with a neuroimaging study? 0

Please describe:

_____

e) Other issues?

Please describe:

_____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? ____ 0 _____

Late cranial US? _____ 0 _____

Brain MRI? _____ 0 _____

Thank you for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!

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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301-496-3790 (FAX)

higginsr@mail.nih.gov

--

From: Susan Hintz
To: Angelita Hensman
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT MRI
Date: Friday, December 15, 2006 12:02:10 PM

Angelita

Thanks so much for the incredibly quick response - and for your hard work on this study!

Susan

> Hi Rose,
>
> Here's the info you requested.
>
> Angelita
>
> ---
>
> **From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> **Sent:** Friday, December 15, 2006 11:22 AM
> **To:** Abbot Laptook; Angelita Hensman
> **Cc:** Susan Hintz; Neil Finer
> **Subject:** SUPPORT MRI
>
> HI - A couple things for the SUPPORT MRI Study -
>
> Please respond to the following questions by **DECEMBER 30TH, 2006**
>
> 1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 10
>
> 2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 10
>
> 3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:
>
> a) How many died before reaching the 35-42 week window?
>
> b) How many have not yet reached the window?

c) How many have reached the window, but have not yet been imaged?

d) How many "missed"/were unsuccessful with a neuroimaging study?

Please describe: _____

e) Other issues?

Please describe: _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?

Early cranial US? __9_____

Late cranial US? ____9_____

Brain MRI? _____9_____

Thank you for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!

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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higginsr@mail.nih.gov

From: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook
Cc: Susan Hintz; Neil Finer
Subject: RE: SUPPORT MRI
Date: Friday, December 15, 2006 11:42:07 AM

Hi Rose,
Here's the info you requested.
Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 15, 2006 11:22 AM
To: Abbot Laptook; Angelita Hensman
Cc: Susan Hintz; Neil Finer
Subject: SUPPORT MRI

HI – A couple things for the SUPPORT MRI Study -

-

Please respond to the following questions by **DECEMBER 30TH, 2006**

1) How many patients have been enrolled to date in the **SUPPORT Neuroimaging secondary** at your site? 10

2) How many have completed 35-42 week neuroimaging studies (MRI and CUS) 10

3) If you have enrolled patients that have **not** completed 35-42 week neuroimaging, please tell us:
   a) How many died before reaching the 35-42 week window?
   b) How many have not yet reached the window?
   c) How many have reached the window, but have not yet been imaged?
   d) How many "missed"/were unsuccessful with a neuroimaging study?
      Please describe: _____
   e) Other issues?
      Please describe: _____

4) How many of the following neuroimaging studies have been copied and sent to RTI?
   Early cranial US? __ 9 _____
   Late cranial US? ____ 9 _____
   Brain MRI? _____ 9 _____

****Thank you** for your hard work and dedication on SUPPORT and the Neuroimaging Secondary!**

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Michael Cotten; goldb008@mc.duke.edu; Gantz, Marie
Subject: Re: MISSING SUPPORT ROP OUTCOMES
Date: Friday, December 15, 2006 8:49:42 AM

Thanks, Rose. These lists continue to be extremely helpful.
Kathy

Kathy J. Auten, MSHS
Project Manager
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Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> wrote on 12/14/2006 01:14:07 PM:

> Hi, We are missing a few ROP outcomes for SUPPORT. The DSMC will
> meet in early February and we would like to have as much information
> as possible. Let us know the status and thanks for all the
> continued effort!!!
> Rose
>
>
>
> 19
>
> (b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
> (b) (6)
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> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> 19
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> (b) (6)
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> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> 19
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> (b) (6)
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> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> 19
>
(b) (6)
>

> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> 19
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>(b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
(b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for the left eye.
>
> 19
>
>(b) (6)
>
> No SUPP10 records have been entered even though SUPP09 Question C1
> indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
>
> 19
>
(b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
(b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
>

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

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ira Adams-Chapman; Susie Buchter
Subject: SUPPORT ROP Exams
Date: Thursday, December 14, 2006 4:55:52 PM

Rose,
Per our conversation:
(b) (6) had one eye exam after discharge that was no ROP with vessels between zones II & III. This child then moved to Austin, Texas. The phone number for their new address has been disconnected. The pediatrician that they told us would follow this child said they knew nothing of this child. We have located a friend's number here in Atlanta and they said that the mom and baby had gone back to Mexico and she did not think they would be back. This baby is probably lost. We will call every few months to the friend to see if they know anything new.
Ellen

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]; Gaynelle Hensley; Pablo Sanchez; Walid Salhab
Cc: Abhik Das; Marie Gantz
Subject: Re: Missing ROP for SUPPORT
Date: Thursday, December 14, 2006 4:10:57 PM

Rose,
The most recent Ophthalmology appt. for this SUPPORT baby was missed and is rescheduled for 1/19/07.
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 12/14/2006 11:03 AM >>>
Center

Network

Message

4

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.

Hi,

The above table has one missing ROP outcome for SUPPORT. We would like
to have as much information as possible for the DSMC meeting which will
occur early in February. Thanks for the commitment to the trial and all
you hard work!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP OUTCOME
Date: Thursday, December 14, 2006 3:44:17 PM

Thanks, Rose.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 14, 2006 3:27 PM
To: Wilson, Dianne H
Cc: Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT ROP OUTCOME

Thanks
Rose

From: Wilson, Dianne H [mailto:dhwilson@iupui.edu]
Sent: Thursday, December 14, 2006 3:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP OUTCOME

Re (b) (6) , that baby died and status is reflected on the NGO3 and Suppo9. 77201 is still in house and will check her status.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 14, 2006 1:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B; Wilson, Dianne H
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT ROP OUTCOME

One more:

12 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, December 14, 2006 1:04 PM
To: 'Poindexter, Brenda B'; (dhwilson@iupui.edu)
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT ROP OUTCOME

12 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,
We are missing one SUPPORT ROP outcome. Let us know the status. We would like to have all of the information for the DSMC meeting in early February.

Thanks
Rose

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higginsr@mail.nih.gov

From: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook
Cc: Das, Abhik; Gantz, Marie; Lucy Noel
Subject: RE: SUPPORT ROP OUTCOME
Date: Thursday, December 14, 2006 2:28:36 PM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 14, 2006 1:08 PM
To: Abbot Laptook; William Oh; Angelita Hensman
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT ROP OUTCOME

14	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. "No show" for ophthalmology appointment and F/U appointments. Phone is "out of service". Unable to contact the mom. The ophthalmologist,pediatrician and F/U Clinic have the same phone number. The F/U Clinic has sent letters to the mother with no response. Per the pediatrician's office .....the baby has an appointment tomorrow. They have a note in the chart to have her follow up with the ophthalmologist and also to get her current phone number so we can contact her. We had planned to F/U with the pediatrician's office on Monday.
14	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Next appointment scheduled for 02/15/07
14	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Next appointment scheduled for 01/04/07
14	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. Next appointment scheduled for 01/12/07

We are missing ROP outcomes on the above infants. The DSMC will meet in early February and we would like to have as many outcomes as possible. **THANKS FOR ALL THE HARD WORK THAT YOUR SITE HAS DONE RECRUITING FOR THIS TRIAL!!!**
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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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:
Date: Thursday, December 14, 2006 1:44:55 PM

Rose,

We are making progress. The computer arrived late yesterday afternoon and I am waiting for our Information Services to come by before we can try using it. RTI replaced the hard drive and there are special configuration settings that have to be in place before we can hook it up to our med school system. Jenny said the next montly report will be from the January 2nd transmission, so hopefully our site will look a little better on paper by then.

Have a nice holiday. I hope all is well with you and your family. I will get my introduction to (b) (6) and I am hoping for "kind" weather. (b) (6)

Nancy

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 14, 2006 1:16 PM
To: Michael O`Shea; Nancy Peters
Cc: Das, Abhik; Gantz, Marie
Subject:

20	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Hi,
We are missing the above SUPPORT ROP Outcomes. I know that you folks had a computer transmission problem. If this is still a problem, let us know. Perhaps these can be hand entered as the DSMC will meet in early February.

Thanks for all the effort and continued commitment!!
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: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Maynard Rasmussen; paul.wozniak@sharp.com
Date: Thursday, December 07, 2006 12:13:49 PM

Hi Rose
We are awaiting the final approval from Contracts and Grants and Sharp Mary Birch is also awaiting full approval. Both sites require a letter from you indicating that we have been requested to re-initiate enrollments in SUPPORT, and the secondaries if possible.
I emailed you the letter regarding our funding request.
Hot Topics sounds interesting. My major concerns with COIN are as fellows:
No infants of 24 weeks, inclusion of 28 weekers likely to not be informative. No protocol requirement to use surfactant – I have the protocol and it is silent re: surfactant use or indication which means that COIN did not compare early CPAP to surf but rather to intubation and ventilation. Was data presented re surfactant use?
We will be doing the Cochrane Review for these studies so I will try to get this from Colin.
Hope all is well with you and family.
Neil

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: FW: Subcommittee vote/Support Growth Secondary
Date: Tuesday, December 05, 2006 11:32:19 AM

Hi Rose,
I've not heard back from Dr. Duara regarding the suggestion in the email below based on the following responses from the committee for the Growth study for the two added time points for growth measurement at D/C or 120 days if in house, and late D/C at 127 days:

Dr. Carlo = agreement
Dr. Faix = entirely reasonable
Dr. Poindexter = not unreasonable but would like clarification on how the extra data would be used

Dr. Laptook = excused himself from the vote since they are no longer a participating center

Dr. Das = requested clarification on how the extra data would be used
Dr. Ehrenkranz = "...I think that being able to standardize growth measures at specific time points is most important; that is why 36 weeks PMA is actually better than discharge. Brenda's growth outcomes paper comparing early vs late AA intake reported outcomes at 36 weeks. The values at discharge are key if discharge comes before 36 wks PMA. We get growth measures at status if the infants are still in-house for the GDB. I do not know how we would use values obtained after that point in research report; in fact, we could question how we would use values obtained at status, since that will also be a variable PMA time point. Therefore, I agree with Abhik's point..."

Drs. Finer, Walsh, Yoder, Schibler, and Nancy Newman and Wade Rich have not weighed in. Should I give it a couple more days or make the changes?

Thanks,
Kris

From: Zaterka-Baxter, Kristin
Sent: Friday, December 01, 2006 4:00 PM
To: 'sduara@miami.edu'; 'CNavarrete@med.miami.edu'
Cc: Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: FW: Subcommittee vote/Support Growth Secondary

Hi,
Should the manual be revised to say:

"...measurements at birth, postnatal age 7, 14, 21, and 28 days, 32 weeks postmenstrual age, 36 weeks postmenstrual age **or** discharge **whichever comes first.**

Noting that infants who are in hospital >120 days, or death occurs after 36 wks PMA but prior to 120 days of hospitalization, will have growth measures per GDB.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Friday, December 01, 2006 2:50 PM
To: richard.ehrenkranz@yale.edu; bpoindex@iupui.edu; Das, Abhik; Zaterka-Baxter, Kristin
Cc: higginsr@mail.nih.gov; Navarrete, Cristina
Subject: Re: Subcommittee vote/Support Growth Secondary

Thanks for the input. Since neither Rich nor Brenda recall criticism, it must have been discussion in GDB subcommittee I'm recalling. At any rate, I'm OK with dropping this measure if it is likely to be unused data added to coordinator time and effort.
Shahnaz

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Richard Ehrenkranz <richard.ehrenkranz@yale.edu>
To: Duara, Shahnaz; Brenda Poindexter <bpoindex@iupui.edu>; Abhik Das <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>
Cc: Rosemary Higgins <higginsr@mail.nih.gov>; Navarrete, Cristina
Sent: Fri Dec 01 13:26:57 2006
Subject: RE: Subcommittee vote/Support Growth Secondary

Hi,
My apologies for not joining into this discussion sooner. I think that being able to standardize growth measures at specific time points is most important; that is why 36 weeks PMA is actually better than discharge. Brenda's growth outcomes paper comparing early vs late AA intake reported outcomes at 36 weeks. The values at discharge are key if discharge comes before 36 wks PMA. We get growth measures at status if the infants are still in-house for the GDB. I do not know how we would use values obtained after that point in research report; in fact, we could question how we would use values obtained at status, since that will also be a variable PMA time point. Therefore, I agree with Abhik's point.
I hope that these comments are helpful.

Shahnaz: I was also unaware of criticism for not having discharge growth information for infants with prolonged stays. Can you be more specific?

Again, I apologize for my tardiness.

Richard

At 10:37 AM 11/30/2006, Duara, Shahnaz wrote:

It's mainly data to answer questions, if they should come up at review. As you say, it's only a small group of infants who will need the extra measures. I would keep as is, but am open to change if other sc members would rather drop this data collection time point.
Shahnaz

From: Brenda Poindexter [mailto:bpoindex@iupui.edu <mailto:bpoindex@iupui.edu>]
Sent: Thursday, November 30, 2006 10:09 AM
To: Duara, Shahnaz; Abhik Das; Zaterka-Baxter, Kristin
Cc: Rosemary Higgins; Navarrete, Cristina; Richard Ehrenkranz
Subject: Re: Subcommittee vote/Support Growth Secondary

Shahnaz,

I guess I wasn't aware that we have received criticism for not having discharge growth info on the babies that have prolonged stays - I would think it would be more important to focus on the time points where you can capture the greatest number of babies in the cohort rather than adding another measurement point that will only be relevant for a few of the group. Having said that, I can't imagine that adding another set of

measurements for such a small group of babies will be that time consuming either, so I don't think it is unreasonable to add - but I think Abhik's question about how you will use the additional points in the analysis deserves consideration.

Brenda

According to Rich and Brenda, that has been a criticism of NRN growth papers from reviewers - lack of discharge growth information. It is information mostly for the reviewers, in my opinion.

Let's see what Rich and Brenda think

Shahnaz

From: Das, Abhik [mailto:adas@rti.org] <mailto:adas@rti.org%5d>

Sent: Monday, November 27, 2006 10:21 AM

To: Zaterka-Baxter, Kristin

Cc: Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz

Subject: RE: Subcommittee vote/Support Growth Secondary

Why do we need #3 and how is it going to be used in the analysis?

From: Zaterka-Baxter, Kristin

Sent: Monday, November 27, 2006 10:16 AM

To: 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; 'mcw3@cwru.edu'; 'wcarlo@peds.uab.edu'; 'Roger.Faix@hsc.utah.edu'; 'nfiner@ucsd.edu'; 'Bradley.Yoder@hsc.utah.edu'; Gantz, Marie; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'; Huitema, Carolyn Petrie

Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; 'sduara@miami.edu'; 'Ruth Everett (Reverett@med.miami.edu)'; 'CNavarrete@med.miami.edu'

Subject: Subcommittee vote/Support Growth Secondary

Hi all,

A recent question about obtaining anthropometric measurements on infants still in hospital at 120 days prompted the following suggested revisions to the Support Secondary Growth study for which we would like your review and comments by Wednesday, November 29th if possible:

Currently per protocol, weight, length and head circumference will be measured at birth, postnatal age 7, 14, 21, and 28 days, 32 weeks postmenstrual age, 36 weeks postmenstrual age and discharge. The next study measurements are obtained during the 18-22 month follow up.

Suggestions/clarifications and additional time points:

Weight, length and head circumference should be obtained at:

1) Discharge when it occurs earlier than 120 days

2) Status (120 days) for all babies in-house at that time

3) Late discharge (> 127 days) for babies with a prolonged stay

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP

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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: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; goldb008@mc.duke.edu; Gantz, Marie
Subject: Re: MISSING ROP OUTCOMES
Date: Thursday, November 30, 2006 4:32:38 PM

Reports pending from outside MD: (b) (6)

Reports from all available visits received from outside MDs: (b) (6)
Note that (b) (6) has regressed ROP stage 1 at last visit a year ago and has refused to return to outside MD or Duke for eye or clinic appointments. Has an appointment in the system for Jan 2007 (b) (6) has not been seen here or anywhere else. Will email Dale re: how she wants to handle these records.

Completed (b) (6)

Died prior to discharge; record as complete as possible: (b) (6)

I am working on getting these into the system.

Kathy J. Auten, MSHS
Project Manager
NICHD Neonatal Research Network Trials
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

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

11/17/2006 04:16 PM

To <goldb008@mc.duke.edu>, "Kathy J Auten" <auten002@mc.duke.edu>
cc "Gantz, Marie" <mgantz@rti.org>, "Das, Abhik" <adas@rti.org>
Subject MISSING ROP OUTCOMES

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
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SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	19 (b) (6)

Hi
The above infants are missing ROP outcome status for SUPPORT. Can you let us know what the status is?
Thanks for all the effort.
Rose

Rosemary D. Higgins, M.D.
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Shankaran, Seetha
To: Walsh, Michele; Neil Finer; adas@rti.org; Langer, John C.; kpoo@rti.org
Cc: "Wally_Carlo_M.D." <; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hypercarbia abstract
Date: Wednesday, November 29, 2006 3:28:36 PM

Michele
re your Q # 1----I suggest you use hypercarbia definition of 55 rather than 50. Per John that increases your # in the reference group, and I agree 30 is too small

Q # 2---I really do not think in a retrospective analysis with limited data collection that we can figure out why they are hypercarbic, certainly we cannot confirm if a strategy of permissive hypercapnia was being used. We can look at measures of ventilatory support, need for blood gas measurements etc , adjust for bwt, gestational age . I think we can look at impact of hypercarbia with the limitations of the data set

Hope this helps
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

From: Walsh, Michele [mailto:Michele.Walsh@uhhospitals.org]
Sent: Tuesday, November 28, 2006 8:27 AM
To: Neil Finer; adas@rti.org; Langer, John C.; kpoo@rti.org
Cc: Shankaran, Seetha; "Wally_Carlo_M.D." <; "Higgins_Rosemary_" <
Subject: RE: Hypercarbia abstract

sorry: attachment here.
Michele

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, November 27, 2006 7:16 PM
To: Walsh, Michele; adas@rti.org; Langer, John C.; kpoo@rti.org
Cc: "Shankaran_Seetha" <; "Wally_Carlo_M.D." <; "Neil_Finer" <; "Higgins_Rosemary_" <
Subject: RE: Hypercarbia abstract

Hi Michele

There was no copy of the abstract attached.
I believe that within most practices a PaCO2 of < 55 is probably considered normal. Do you have mean airway pressure as a measure of ventilator management?
If people were trying to deal with or prevent such a high PaCO2 one may expect a higher RR or PIP which may be reflected in the MAP. I realize that this is not always so as the denominator of MAP is ITime + ETime. If infants with elevated PaCO2 have higher RR or MAP, this may relate to the causality ie significant lung disorder vs acceptance of higher values. We would ordinarily not change the vent for a PaCO2 of 55 or 58 and thus we might expect that the MAP of 6-8 is not indicative of increasing ventilation. Would this be worth an evaluation if you have such data at the time of the PaCO2. The other issues would be the presence of an air leak, PIE etc and the FiO2. A low FiO2 would argue against significant lung problems and a permissive approach. You could also take Wally;s suggestion to look at PaCO2 as a continuous variable or look at different cut points ie 60, & 65. In actual practice units tend to work around a specified value or range. I would be happy to look at the actual abstract.
Be well
Neil

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, November 27, 2006 2:58 PM
To: adas@rti.org; Langer, John C.; kpoo@rti.org
Cc: Shankaran_Seetha; Wally_Carlo_M.D.; Neil_Finer; Higgins_Rosemary_
Subject: Hypercarbia abstract

Hi All:
Wanted to bring you up to speed on the hypercarbia abstract.
John and I have had a number of emails and calls about this abstract.
We have encountered a data analysis issue that is thorny- and we believe will benefit from your wise input.
Attached is a draft of the abstract to give you context.
Purpose: Evaluate the safety and efficacy of hypercarbia in the first week of life in ELBW.
Method: We are using similar time weighted methodology as used by Seetha in the hypocarbia abstract. We intend to use a reference grp as the normative grp for acute and longer term outcomes.
However: <u>OUR PROBLEM #1</u>: there are only 30 babes with CO2 35-50 which we defined as nml.
118 have a combination of normocarbia and hypocarbia. 419 have various exposures to hypercarbia.
I am uncomfortable with using a reference grp of only 30 as the gold standard.
1. Is anyone else troubled by such a small comparator group?
2. Would it be legitimate to expand the group perhaps by increasing our hypercarbia definition to >55?

<u>PROBLEM #2:</u>
Logically, there are two reasons why children may be hypercarbic: either bc a permissive hypercapnic strategy is being used, or because their severity of illness is such that they are hypercarbic.
We have no information on intent of the treating physician. It is unclear to me how to resolve this issue. We can adjust in analysis for bwt or GA to attempt to correct for severity of illness.
Is this a fatal flaw such that we should not proceed with the abstract? Or is there still value in knowing the impact of hypercarbia regardless of the mechanism?
John and I await your thoughts. PLs reply to all.

Michele Walsh

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR 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.

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR 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: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: WEEFIM
Date: Tuesday, November 28, 2006 6:04:22 PM

Consent is not an issue for us. Sharp may have different issues.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 28, 2006 2:56 PM
To: Wade Rich
Cc: Neil Finer
Subject: Re: WEEFIM

You will need to have GDB data. I can get a sample consent from Rochester for inositol so that you can embed the GDB consent into the Support consent - let me know - I meant to call you about this!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wade Rich <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer <nfiner@ucsd.edu>
Sent: Tue Nov 28 17:43:47 2006
Subject: RE: WEEFIM

Rose,
It occurs to me we will have the same problem IOWA was having re: no GDB number but a SUPPORT enrollment. Please let me know how you and RTI decided to work that out. I am going to try and figure out what data components of GDB are necessary to carry out SUPPORT so that we can limit unnecessary data collection.
Wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 28, 2006 12:27 PM
To: bss5@cwru.edu; Janet.Morgan@childrens.com; Teresa.Gratton@uc.edu; ldrichar@iupui.edu; Elaine Romano; lnoel@wihri.org; M. Bethany Ball; Vivien Phillips; Hust, Diane; Melody B Lohmeyer; Martha G. Fuller; Everett, Ruth; Wade Rich; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu; apappas@med.wayne.edu; adusick@iupui.edu; Betty_Vohr@brown.edu;

cbauer@peds.med.miami.edu; (b) (6) [redacted]
Gary_myers@URMC.Rochester.edu; Ira Adams-Chapman; steichjj@email.uc.edu; mperalta@peds.uab.edu; golds005@mc.duke.edu; Robert Dillard; Roy Heyne; Susan Hintz; Yvonne Vaucher; Karen.Osborne@hsc.utah.edu; Angelita Hensman; afurey@tufts-nemc.org; Becky bara; Bethany Ball; Cathy Grisby; Conra Backstrom; Diane Wilson; Ellen Hale; Georgia McDavid; karen-johnson@uiowa.edu; Kathy Auten; Lucy Miller; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; susan.tepper@hsc.utah.edu
Cc: Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: FW: WEEFIM

Hi

The WEEFIM will not be done for extended hypothermia. Please forward this to your psychologists and other personnel at your site.

Thanks

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 17, 2006 12:53 PM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; Ambal (ambal@uab.edu); Av Fanaroff (aaf2@po.cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Ivan Frantz'; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); 'Kristi Watterberg'; Kurt Schibler (Kurt Schibler [kurt.schibler@cchmc.org]); Michael Cotten (cotte010@mc.duke.edu); 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; papile@unm.edu; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (walid.salhab@utsouthwestern.edu); (apappas@med.wayne.edu); Anna Dusick (adusick@iupui.edu); Betty Vohr ('Betty_Vohr@brown.edu'); Charlie Bauer (cbauer@peds.med.miami.edu); Dee WIlson (b) (6) [redacted]; 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'; Yvonne Vaucher (Yvonne Vaucher)
Cc: Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; Newman, Jamie
Subject: WEEFIM

Hi

Due to a need for a complicated licensing agreement that potentially

includes data access, pre-publication review of manuscripts, and other issues, the decision has been made to consider deletion of the WEEFIM from the extended hypothermia follow up protocol, unless the licensing agreement can be simplified. The decision was reached after discussion among Drs. Das, Shankaran and myself. A discussion will occur on the scheduled steering committee call on 11/28.

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Susie Buchter; Anthony Piazza
Subject: SUPPORT
Date: Monday, November 27, 2006 1:10:28 PM

Dear Rose,
This is to let you know that we are completing a SAE for SUPPORT study patient (b) (6) This infant developed NEC on day 25 and was taken to surgery for resection on day 26. I have spoken with Dr. Buchter and the event is not related to the study. Medwatch and summary will be coming to you. Infant was in the treatment group with an orange monitor.
Ellen

From:	Zaterka-Baxter, Kristin
To:	Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; alaptook@wihri.org; mcw3@cwru.edu; Roger Faix; nfiner@ucsd.edu; bradley.yoder@hsc.utah.edu; Nancy Newman; Wade Rich
Cc:	Das, Abhik; Gantz, Marie; Huitema, Carolyn Petrie
Subject:	FW: Subcommittee vote/Support Growth Secondary
Date:	Monday, November 27, 2006 12:52:19 PM

Please see Dr. Carlo's response below.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, November 27, 2006 10:18 AM
To: Zaterka-Baxter, Kristin
Subject: RE: Subcommittee vote/Support Growth Secondary

agreement

-----Original Message-----
From: "Zaterka-Baxter, Kristin" <kzaterka@rti.org>
To: "kurt.schibler@cchmc.org" <kurt.schibler@cchmc.org>; "alaptook@WIHRI.org" <alaptook@WIHRI.org>; "mcw3@cwru.edu" <mcw3@cwru.edu>; "wcarlo@peds.uab.edu" <wcarlo@peds.uab.edu>; "Roger.Faix@hsc.utah.edu" <Roger.Faix@hsc.utah.edu>; "nfiner@ucsd.edu" <nfiner@ucsd.edu>; "Bradley.Yoder@hsc.utah.edu" <Bradley.Yoder@hsc.utah.edu>; "Gantz, Marie" <mgantz@rti.org>; "nxs5@cwru.edu" <nxs5@cwru.edu>; "wrich@ucsd.edu" <wrich@ucsd.edu>; "Huitema, Carolyn Petrie" <petrie@rti.org>
Cc: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; "Das, Abhik" <adas@rti.org>; "sduara@miami.edu" <sduara@miami.edu>; "Reverett@med.miami.edu" <Reverett@med.miami.edu>; "CNavarrete@med.miami.edu" <CNavarrete@med.miami.edu>
Sent: 11/27/2006 9:15 AM
Subject: Subcommittee vote/Support Growth Secondary

Hi all,

A recent question about obtaining anthropometric measurements on infants still in hospital at 120 days prompted the following suggested revisions to the Support Secondary Growth study for which we would like your review and comments by Wednesday, November 29th if possible:

Currently per protocol, weight, length and head circumference will be measured at birth, postnatal age 7, 14, 21, and 28 days, 32 weeks

postmenstrual age, 36 weeks postmenstrual age and discharge. The next study measurements are obtained during the 18-22 month follow up.

Suggestions/clarifications and additional time points:

Weight, length and head circumference should be obtained at:

1) Discharge when it occurs earlier than 120 days

2) Status (120 days) for all babies in-house at that time

3) Late discharge (> 127 days) for babies with a prolonged stay

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Mcdavid, Georgia E
Subject: FW: Oximeters
Date: Wednesday, November 22, 2006 3:01:29 PM
Attachments: Benefits Burdens and Basis for NIC Marco Island.ppt

---

Rose, while I reviewed the award, I didn't go through the justification that arrived later and missed the funds awarded for additional oximeters. Dhiren missed it as well...so we didn't appreciate that funds had been provided. Just as well, given that Georgia thinks we can get by without them. No chance, I assume, of using some of such funds (or modest other funds) for the kind of neonatal epi position for the Network that we have discussed. Kathleen and I are ready to make a change if you are.

You will be interested in attached talk (actually just the 1st 52 slides; ignore the rest) given at the Mead Johnson Marco Island on benefits and burdens of intensive care (describing the findings that Nehal, John Langer, and I expect to submit to NEJM as soon as John can clear the last SPR abstract off his desk and we can tie up the last few loose ends.) No handouts provided so I'm being careful not to jeopardize submission to NEJM.

I have been asked to give the Silverman lectureship at the SPR (Yes, I got goose bumps and immediate anxiety that I wouldn't give a talk worthy of his name.) In thinking about this talk, I may well devote a substantial part to findings of these analyses. You and I previously discussed providing on the Network website a way that clinicians could enter a baby's findings (GA, BW, antenatal steroid status, single vs multiple status) and be provided an estimate of the likelihood of survival, survival without impairment, or survival without profound impairment assuming outcomes like those in the Network. At the time we discussed it, you agreed it would be a good idea and that it could be updated at intervals. John Langer has worked to make the next set of analyses more automated.

What would you think about my announcing during the Silverman talk that the Network will provide this on its website in honor of Bill? Is that something you might see as a good thing? Given his efforts to promote evidence based decision making in the use of intensive care, I would think it would be a neat match between Bill's teachings and Network accomplishments and service.

Have a great thanksgiving, 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: Desai, Dhiren H
Sent: Monday, November 20, 2006 11:04 AM
To: Tyson, Jon E
Cc: Mcdavid, Georgia E; Reardon, Alice J
Subject: RE: Oximeters

Dr Tyson,

On checking more, we did get the dollars awarded to buy 10 oximeters. These funds were awarded as a part of our big capitation award of $503,310 dated 8/10/05. We spoke to Georgia this morning and she thinks we do not need to purchase these oximeters.

We never received a separate email or a memo indicating the availability of these funds. It was totally overlooked by us as it was not a separate budget item.
To-date we have not purchased these oximeters.

Dhiren

From: Tyson, Jon E
Sent: Monday, November 20, 2006 10:15 AM
To: Desai, Dhiren H
Cc: Mcdavid, Georgia E
Subject: FW: Oximeters

Will you check into these funds?

Jon E. Tyson, MD, MPH
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Houston, TX 77030
voice 713-500-5651
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 20, 2006 9:20 AM
To: Tyson, Jon E
Subject: Oximeters

Jon
We had awarded additional dollars in 2005 for oximeters (10)– did your site purchase them?
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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Benefits, Burdens, & Basis for Decisions to Initiate Intensive Care for Extremely Premature Infants: An Interactive Presentation

Jon E. Tyson, MD, MPH
Center for Clinical Research
& Evidence-Based Medicine
UT Houston

What is lowest GA* (GA threshold) at which you feel NIC** should ordinarily be initiated

-if parent(s) oppose such care?

-if parent(s) request such care?

*GA = gestational age (postmenstrual age) by best obstetric estimate

**Newborn intensive care using mechanical ventilation if needed to prevent death

Is there any factor (e.g., race) that would cause you to change these thresholds (and if so, by how much)?

T or F Most neonatologists use GA thresholds in deciding whether to initiate NIC. While these vary, the care of infants born at 21-25 weeks may be dramatically changed by an error in assessing GA of only 1-2 weeks.

T or F For infants in this GA range, as at other GAs,

___ The error* of using LMP (or LMP + 2 wks) to estimate the duration of pregnancy is ±1-2 wks when the dates are reported as certain.

__ The error of using early sonograms is ±1 wk

___ Pediatric estimates of GA have an error* of ±2-3 wks and should be used when they differ from obstetric estimates by this amount.

*Error = ±2 SD for difference between estimate and true value

While only a 1-2 wk difference in GA prompts dramatic differences in care of extremely premature infants, the random error in assessing pregnancy length

- from exact LMP is likely to exceed ±2 wks
- from early sono reported to be ±2 wks
- from ped. assessments may be ±4 wks

Moreover, systematic errors in LMP based estimates result in tendency to underestimate GA of these infants. Systematic errors in pediatric estimate may overestimate GA.

Variation in Cycle Length (and Presumably Ovulation) with Age in Healthy Women

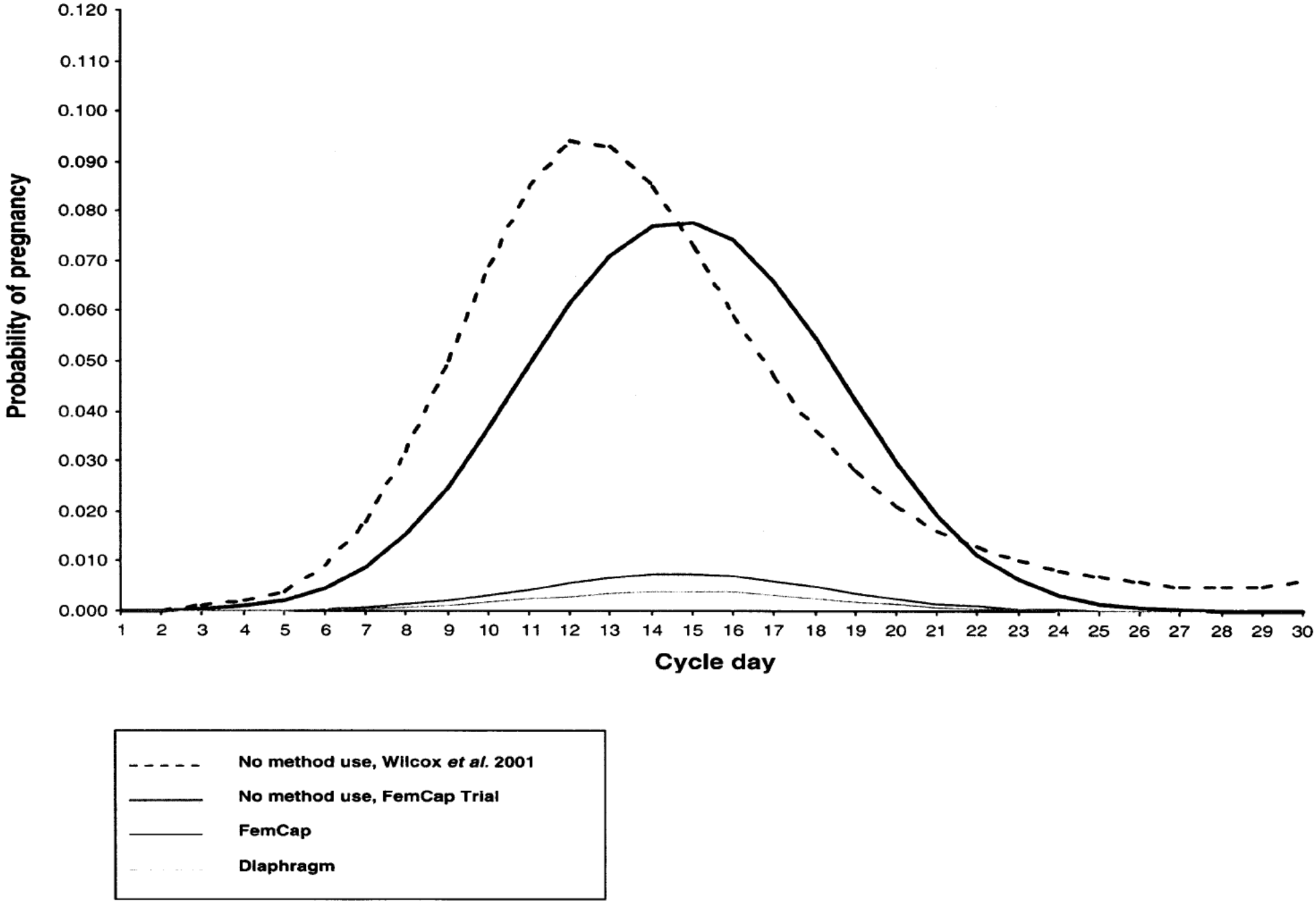
Age	SD
1st two years after menarche	20 d
2-3 years after menarche	10 d
Late adolescence	5 d
Adults	4 d
	(increases at ≥35 y)

At all ages, 2 SD≥ 8 d; Some evidence that intercourse may stimulate ovulation. Pregnancy reported from single intercourse as early as day 2 to as late as day 30.

Width of Fertility Window Relative to Ovulation

In various studies, fertility window found to be 6-10 d long (5-6d before d of ovulation to 0-4 d after)

In study of hormonal metabolites in healthy women (Wilcox et al), only 30% fertile only between 10-17 d; ≥ 10% likelihood in fertility window each d from 6-21 d



Would early ultrasound be a valid method to assess accuracy of a certain LMP as an indicator of pregnancy duration?

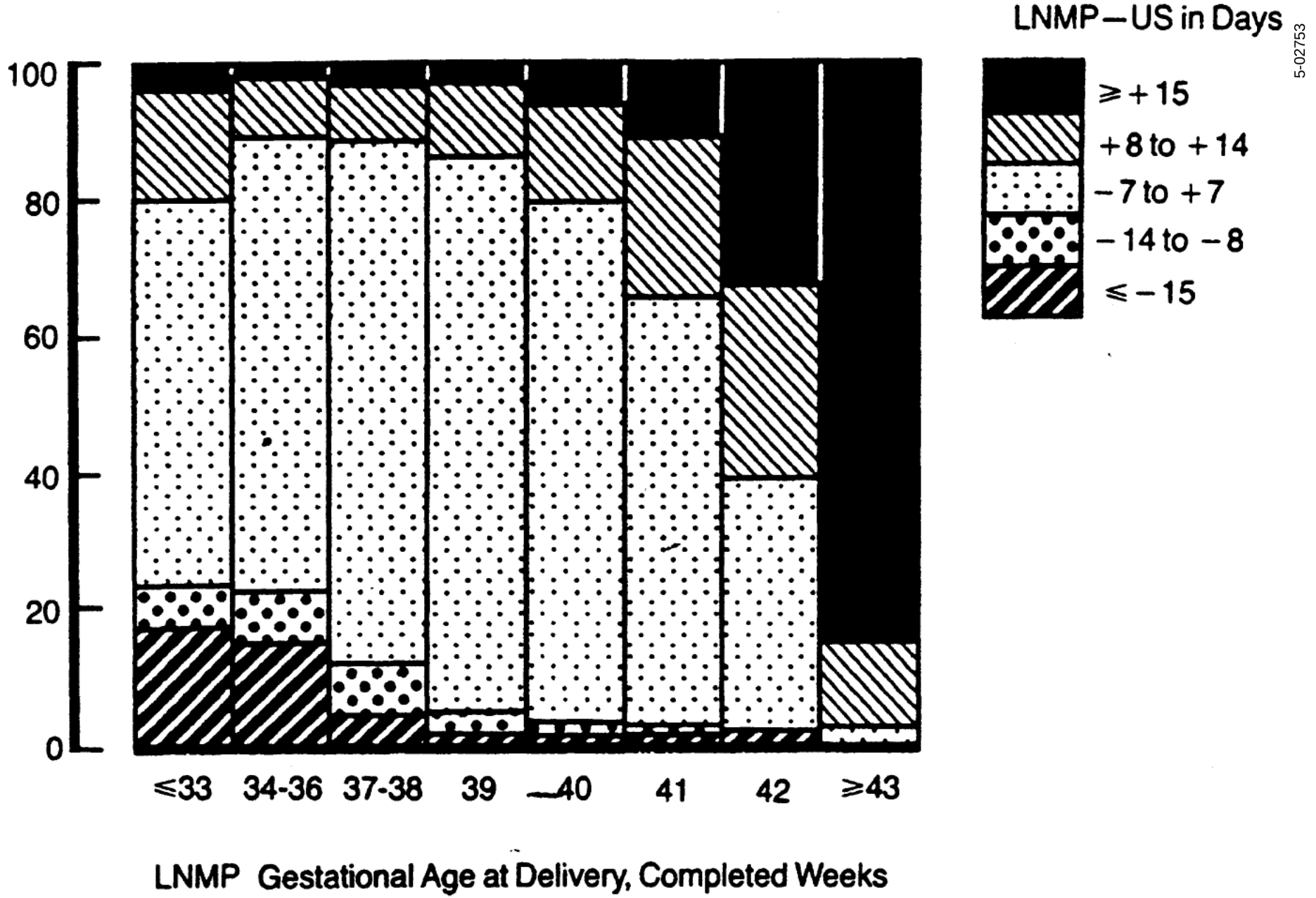


FIG. 1

Graph of actual centiles of birth weight against gestational age of all liveborn single infants.

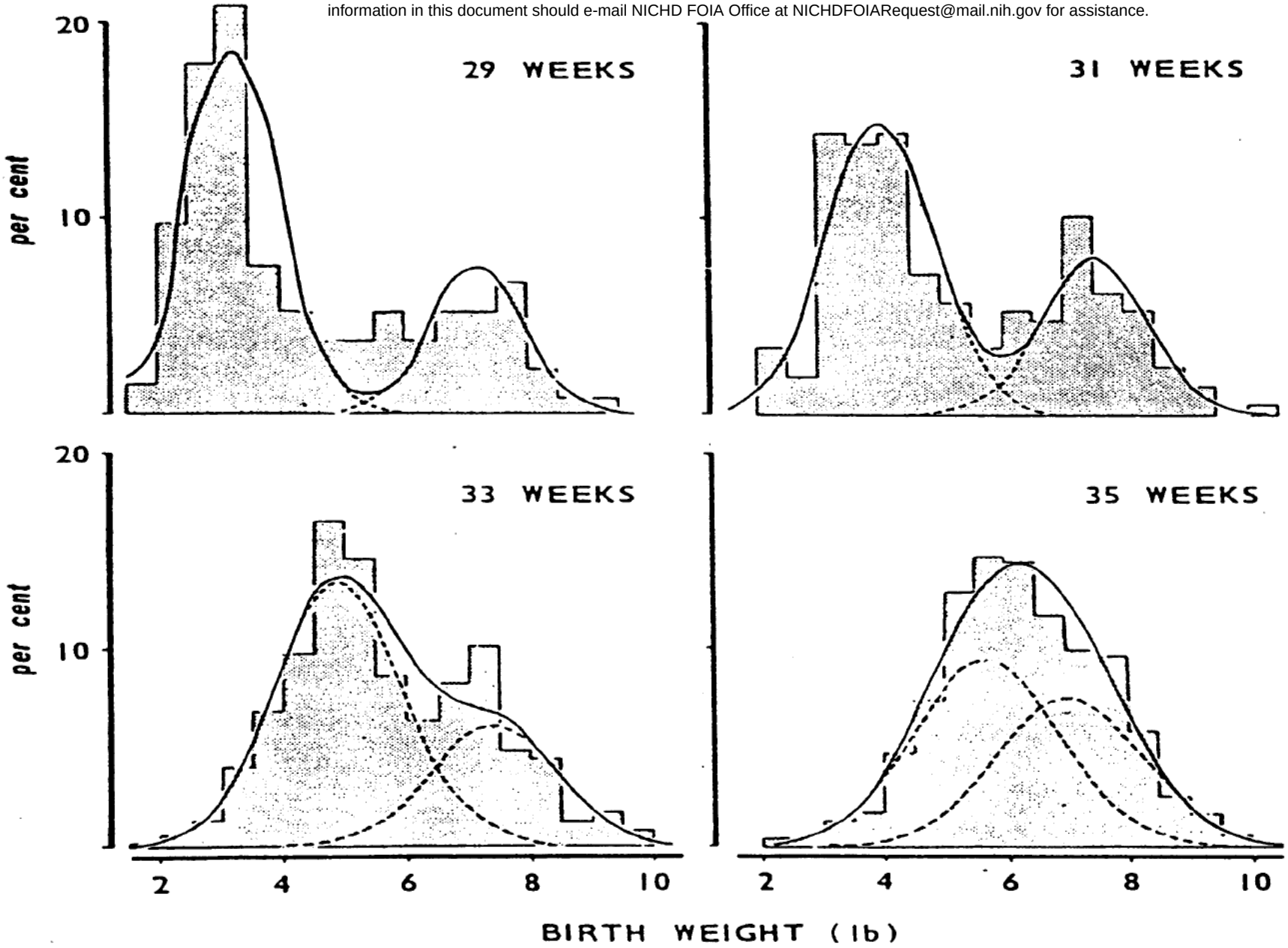


FIG. 3

Histograms of birth weight of male infants born to multiparae at 29, 31, 33 and 35 weeks' gestational age. Superimposed on each histogram are the two normal distributions which describe the observations.

Data points that are most likely to be in error are those that are the most extreme values, and such errors are likely to be in the direction of being too extreme.

Accuracy of sonograms?

Accuracy of early sonograms?

Stated by ACOG to be ±2 wks*

Accuracy of sonograms in L&D likely to be less under "field conditions" and for deliveries at <26 wks.

*ACOG Practice Bulletin "Perinatal care at threshold of viability" (2002)

With advances in commercially available fertility monitors, accuracy of assessing ovulation may be ± 2d

Accuracy of Pediatric GA estimates as a measure of pregnancy length?

Ped. vs. Ob. GA Assessment at 22-27 Weeks with Accurate LMP* in Network

At each week, pediatric estimate varied widely

(95th percentile at 22 wks = 25th percentile at 28 wks)

Mean pediatric estimate (revised Ballard) exceeded Ob estimate by mean of 1.3 – 3.3 wks

Which (Ob or Ped) a more accurate indicator for most pregnancies? Which better reference standard?

*dates certain within 4 d, cycle duration 21-35 d, last 3 cycles normal, no oral contraceptives in previous 3 mo.

T or F or U Though it may later be withdrawn, NIC should be initiated for smallest & most immature infants (unless major anomalies).

Reasons include:

a) GA often in error or uncertain

b) Starting IC allows time to assess response to treatment ("trial of NIC")

c) Most infants who are going to die despite NIC die quickly

d) NIC affords only hope for a good outcome

Mean Age at Death
Network Infants 22-25 wks
by Best Ob Estimate

<2 h for infants who died without receiving mechanical ventilation (n=744)

28 days for infants who died despite mechanical ventilation (n=1414) (~$95,600 total cost/infant @ $3400/day adjusted for inflation from Schmitt et al, 2006)

In all fields of medicine, treatments administered because "only hope for good outcome" have often caused much more harm than good.

Rule of Evidence: Administer a Rx only when there is credible evidence that benefits exceed burdens

Problems in Using Literature to Weigh Benefits & Burdens for Extremely Premature Infants

- Small studies
- Inclusion of outborn infants
- Limited effort to discriminate difference in outcome for subgroups at different risk
- Conventional cost effectiveness analyses problematic & not very meaningful to parents and clinicians
- Self fulfilling prophesy

Assessing Benefits vs. Burdens of NIC for Extremely Premature Infants in NICHD Neonatal Network

Study 1. 1126 inborn infants 501-800 g BW (1994-95); 85% given NIC (JAMA,1996; Clin Perinat 2003). (Outcomes minimally different from most recent).

Benefits: Likelihood of survival; likelihood of survival without severe neonatal morbidity; likelihood of mod/severe NDI

Burdens: Total hospital days "invested" (deaths & survivors) divided by number of infants with good outcome

Addressing the Problem of the Self Fulfilling Prophecy

Maximum potential survival rate* generously estimated by assuming infant who died without MV would have survived at same rate as infants who did receive MV in same risk group.

Maximum potential survival rate without major morbidity estimated using same approach

*with care & conditions in Network units during study

Predictors of Survival in Multivariate Analyses of Infants Given MV

Factor*	Odds Ratio	Estimated BW Equivalent Effect
BW (per 100 G)	0.38	------
Female	0.42	90 g
SGA	0.58	57 g
Antenatal Steroids	0.52	67 g

*Race had no discernible effect

Predictors of Survival Without Grade III/IV ICH In Multivariate Analyses of Infants Given MV

Factor*	Odds Ratio	Estimated BW Equivalent Effect
BW (per 100 G)	0.46	------
Female	0.43	107 g
SGA	0.47	97 g
Antenatal Steroids	0.61	64 g

*Race had no discernible effect

Females in lowest BW group more likely to die without MV than were larger males with a similar estimated likelihood of good outcome with MV

Value judgments unavoidable and implicitly if not explicitly. Considering pain & suffering to infant, resource limitations, & opportunity costs, what do you think is:

-minimum % survival without mod/severe NDI to justify NIC?

-maximum acceptable % survivors of with mod/severe NDI?

-maximum acceptable number of hospital days to salvage one infant without mod/severe NDI?

Findings for 501-600 g infants:

	% Survival*	% Unimpaired Survival*	Hospital Days Invested** /Survivor	Hospital Days Invested** /Unimpaired Survivor
Female	40-52%*	18-24%	138	301
Male	22-37%	4-7%	178	890

*observed – maximum potential % with good outcome

**Hospital days reflects total days invested (for survivors and deaths) divided by total infants with good outcome. If NIC given to infants not previously treated, hospital days /infant with good outcome may be substantially higher

Overall for all 501-800 g infants.

57-65% survival (observed – maximum potential values)

27-31% survival without mod/severe NDI (observed-maximum potential values) (nearly 50% of survivors with NDI).

127 hospital days per survivor

268 hospital days per survivor without mod/severe NDI

Estimated Effects of Universal Rather Than Selective NIC for 501-800 g Infants in Network

Per 100 Infants 501-800 g BW

-Maximum of 8 extra survivors

-Maximum of 3 extra survivors without CLD (0_2 at 36 wks), NEC (surgery), or Grade III/IV ICH

-Maximum of 4 extra survivors without mod/severe NDI at $\geq$18 mo.

- Minimum of 971 extra hospital days.

Need for further study :

- More recent cohort
- Selection based on GA
- Larger sample for subgroup analyses
- Assessment of likelihood of death or profound NDI (Bayley <50 [untestable due to severe handicap] or gross motor function =5): outcomes that may be considered as bad as death.

Weighing Benefits and Burdens of NIC for Extremely Premature Infants in NICHD Neonatal Network

- Analysis 1. 1126 inborn infants 501-800 g BW (1994-1995) (JAMA,1996; Clin Perinatol 2003)

- Analysis 2. 4446 inborn infants 22-25 wks GA weighing 401-1000 g born (1998-2003) (Tyson, Parikh, Langer, et al).

Population*

- Mean GA = 23.8 wks;
- Mean BW = 648 g
- 45% Black; 35% White; 17% Hispanic
- 71% received antenatal steroids
- 83% received NIC (mechanical ventilation),
- 94% outcome assessed at 18-22 mo

*Exclusions: major anomalies; BW <401 or > 1000 g; BW >97th percentile for GA; survival without MV

Among all 22-25 wk infants

48% survived;

39% survived without profound NDI

27% survived without mod/severe NDI

19% survivors had profound NDI;

44% survivors had mod/severe NDI.

Predictors of Outcome Among Infants Given MV

Predictor	Death		Death or Profound NDI		Death or NDI	
	OR*	GA Equivalent Effect§	OR	GA Equivalent Effect§	OR	GA Equivalent Effect§
25 vs. 24 wks	0.62	1.00	0.66	1.00	0.70	1.00
24 vs. 23 wks	0.61	1.02	0.58	1.13	0.56	1.26
23 vs. 22 wks	0.54	1.15	0.50	1.31	0.56	1.25
BW (/100g ↑)	0.60	1.04	0.61	1.08	0.61	1.16
Female	0.64	0.97	0.55	1.19	0.48	1.47
Antenatal Steroids	0.55	1.14	0.54	1.23	0.53	1.33
Singleton	0.77	0.81	0.76	0.87	0.70	1.00

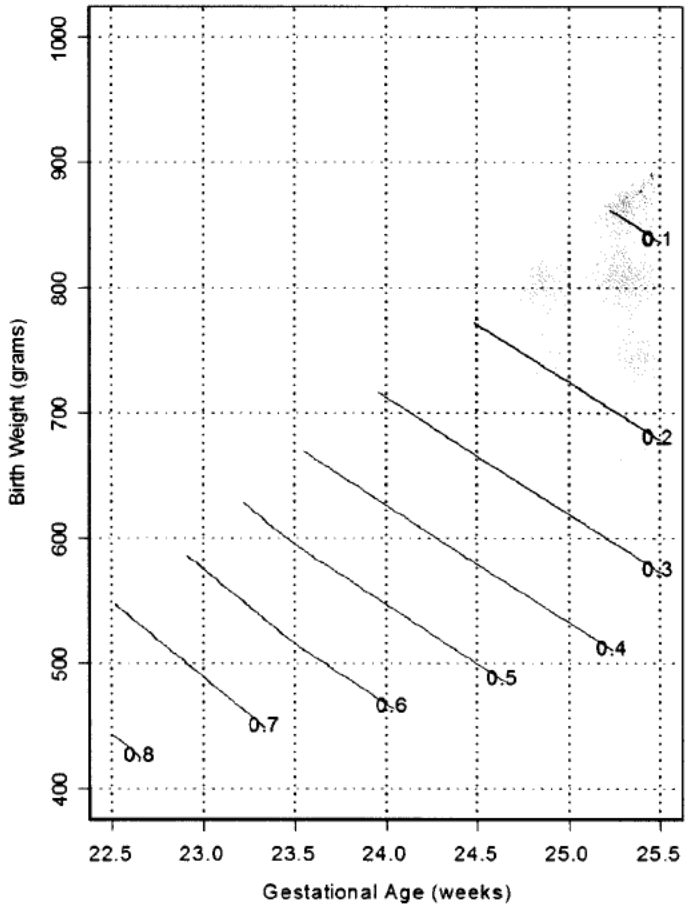
*OR= Odds Ratio § Race unrelated to outcome in univariable & multivariable analyses.

5-02779

Given their immense consequences, why base decisions to administer or forego NIC largely or solely on GA?

Probability of Death - Ventilated Singleton Females

With ANS



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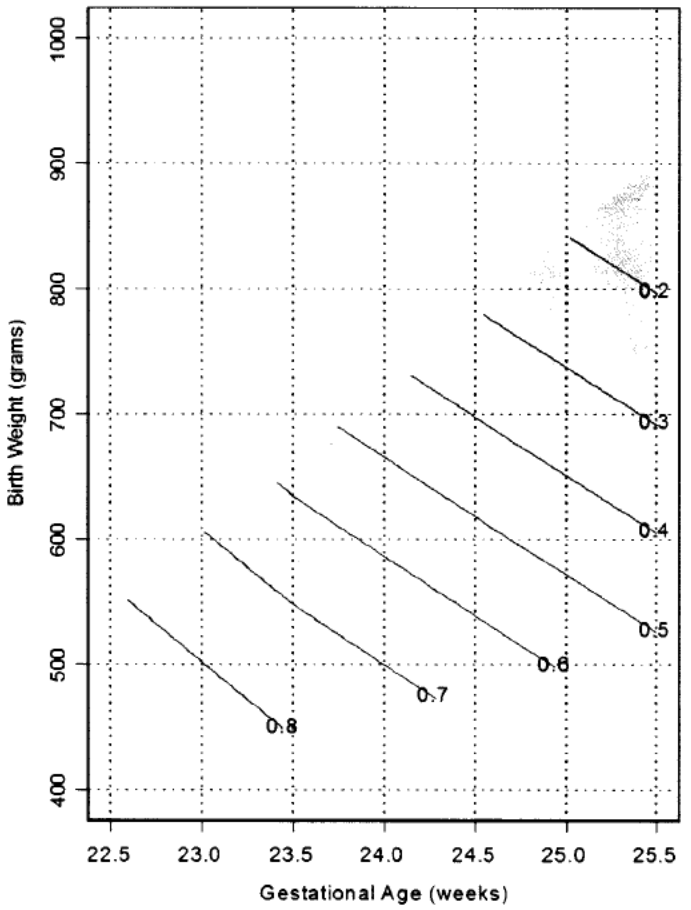
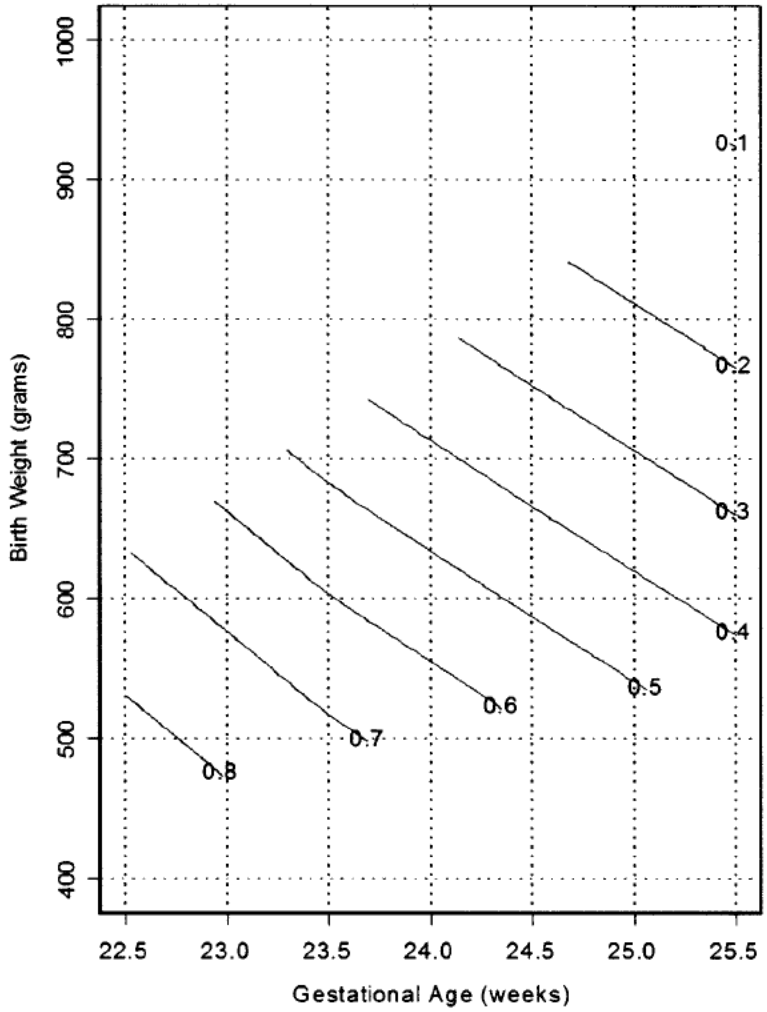


Probability of Death - Ventilated Singleton Males

With ANS



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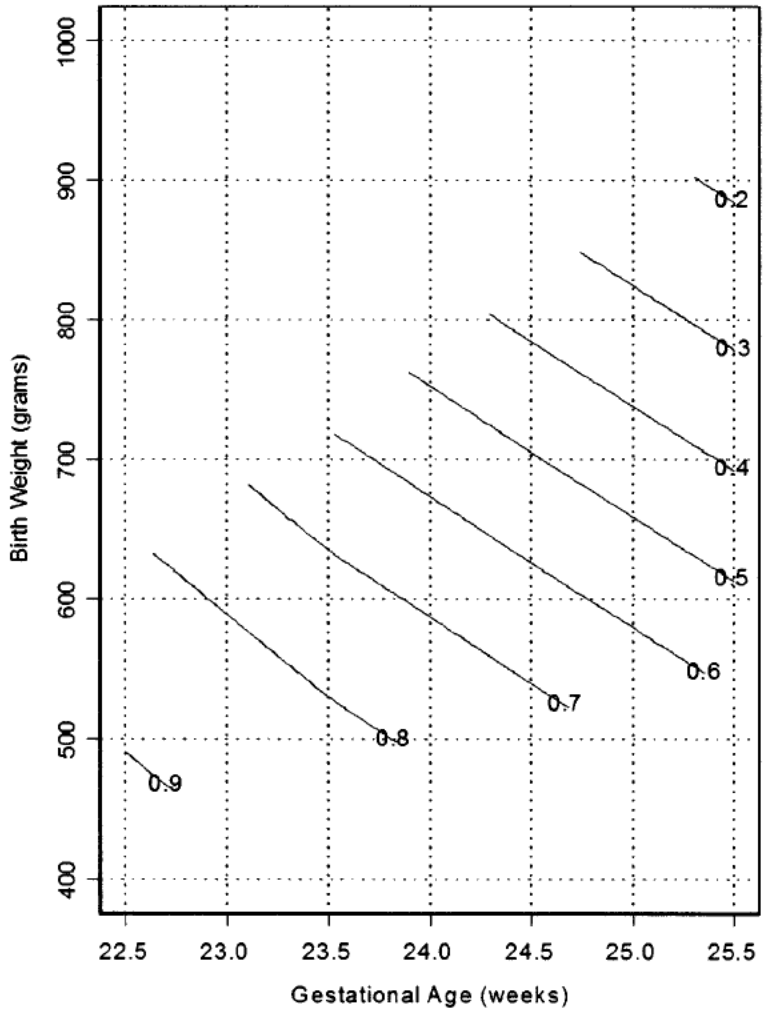
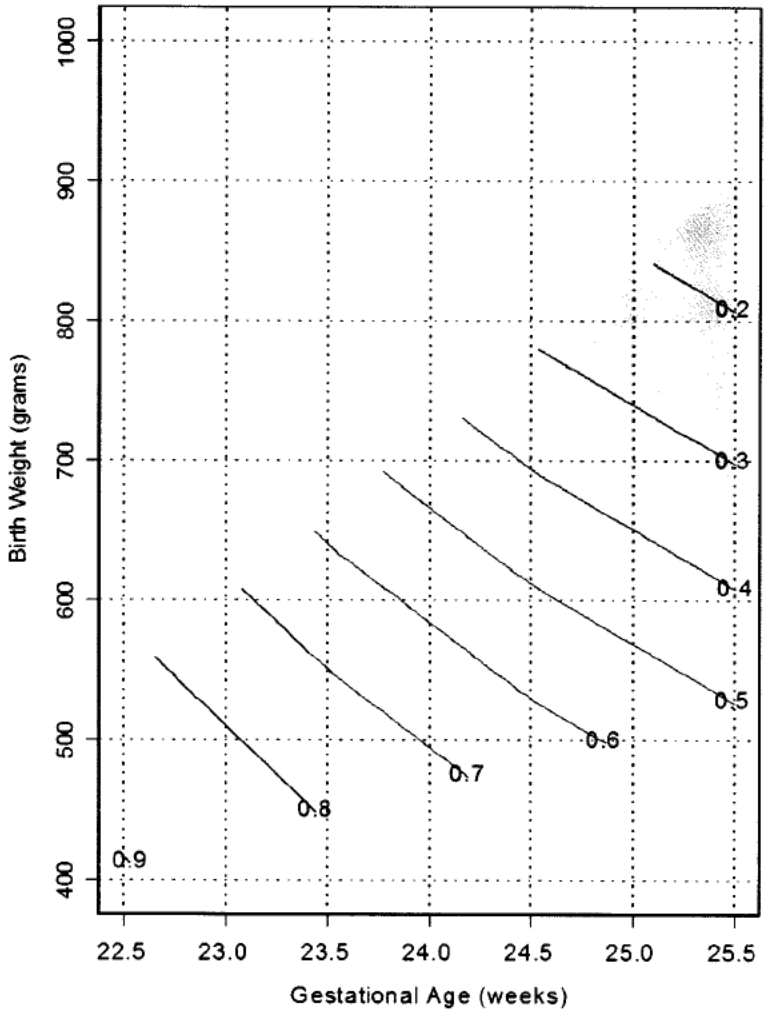


Probability of Death or Profound Impairment
Ventilated Singleton Females

With ANS



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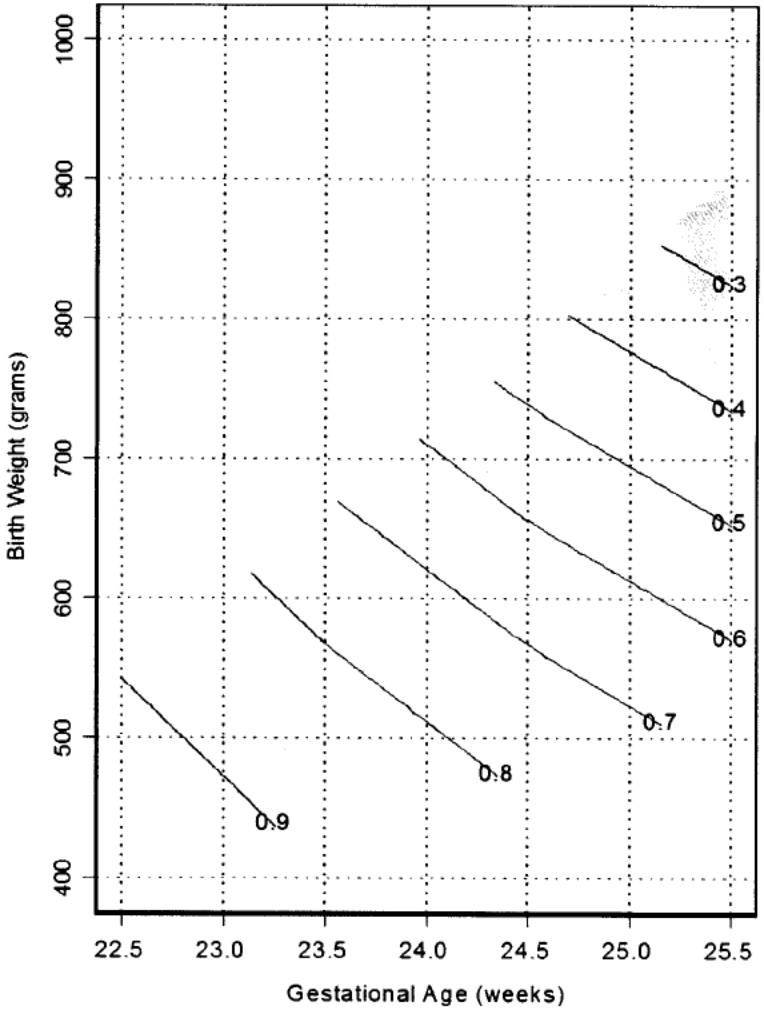

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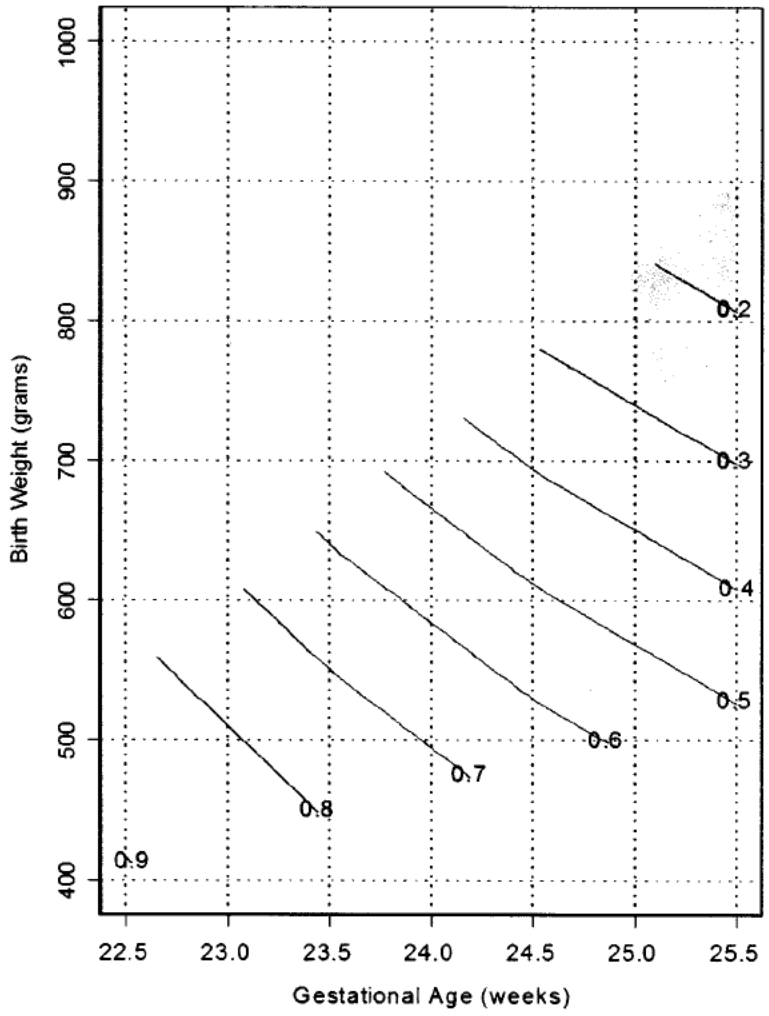
Probability of Death or Profound Impairment
Ventilated Singleton Females

With ANS



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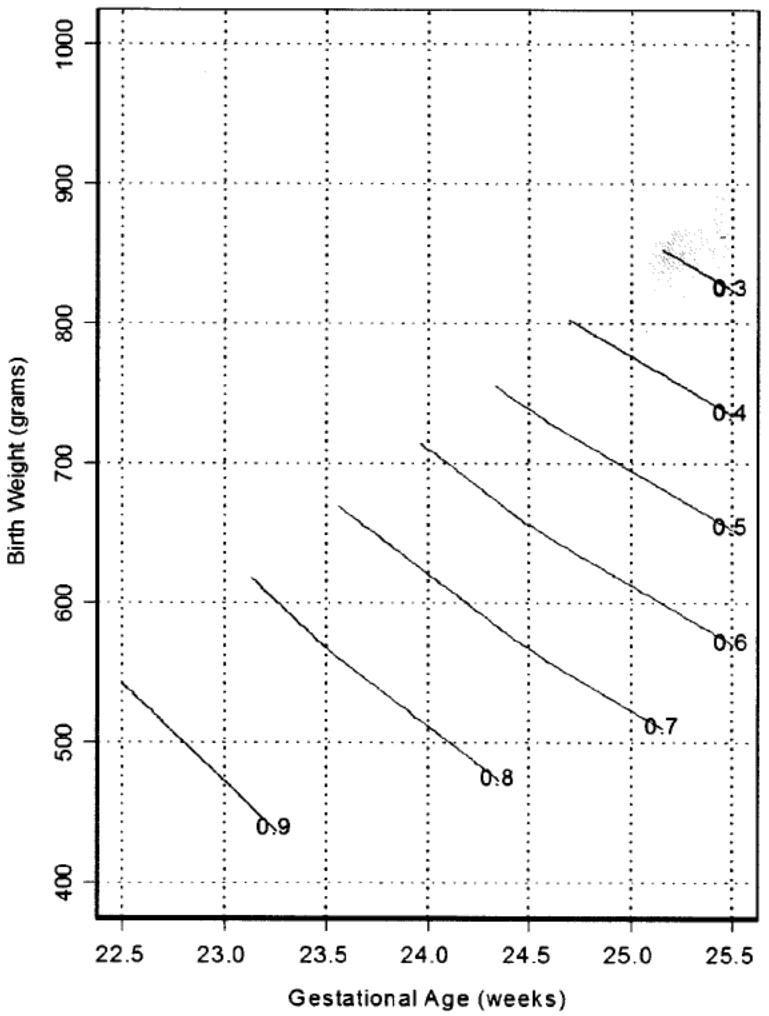

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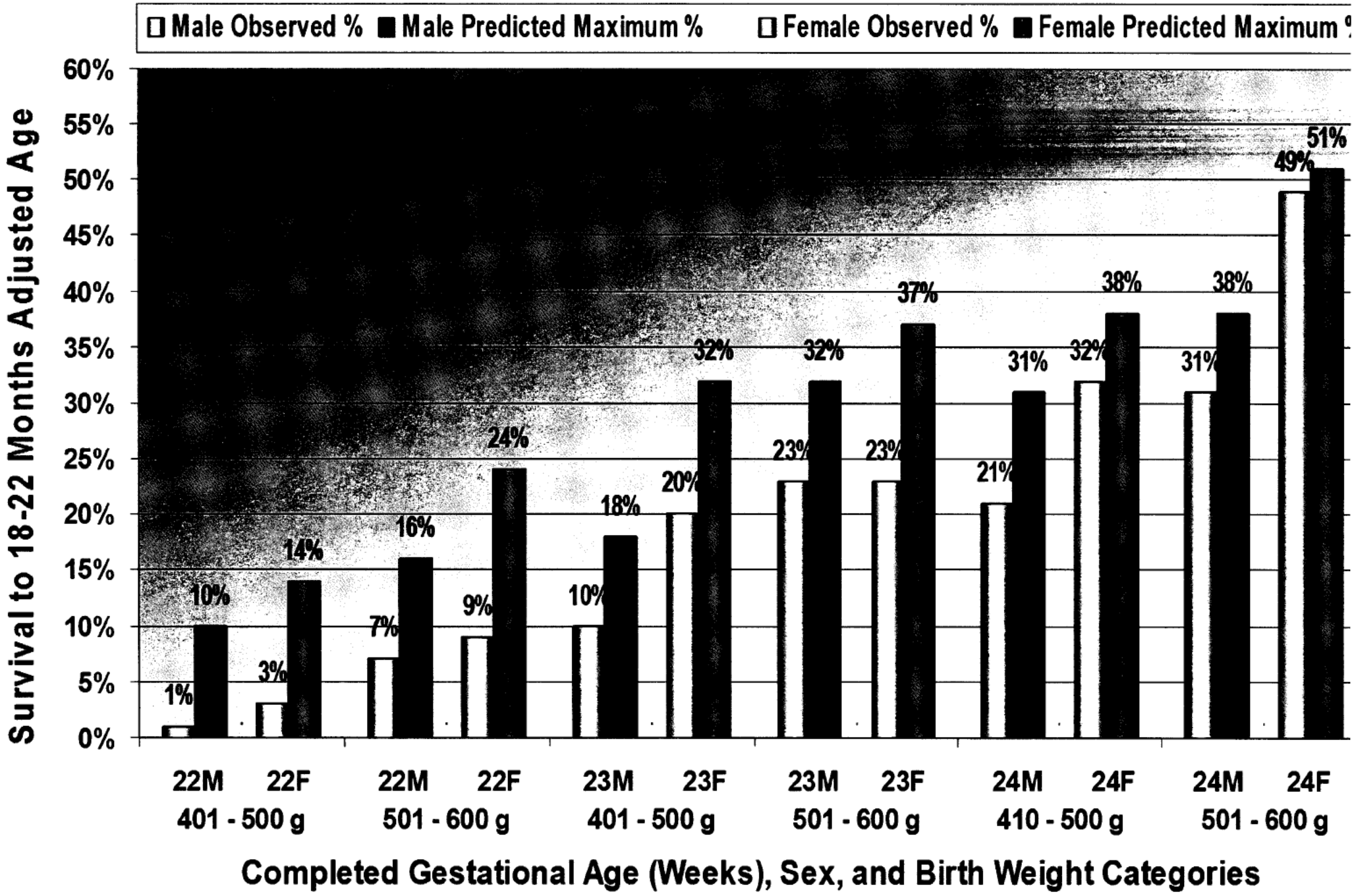
Considering pain & suffering to infant, resource limitations, & costs, what is

- minimum % survival
- minimum % rate of survival without profound NDI
- maximum number of ventilator days justified to salvage one infant without profound NDI?
- maximum number of hospital d justified to salvage one infant without profound NDI?



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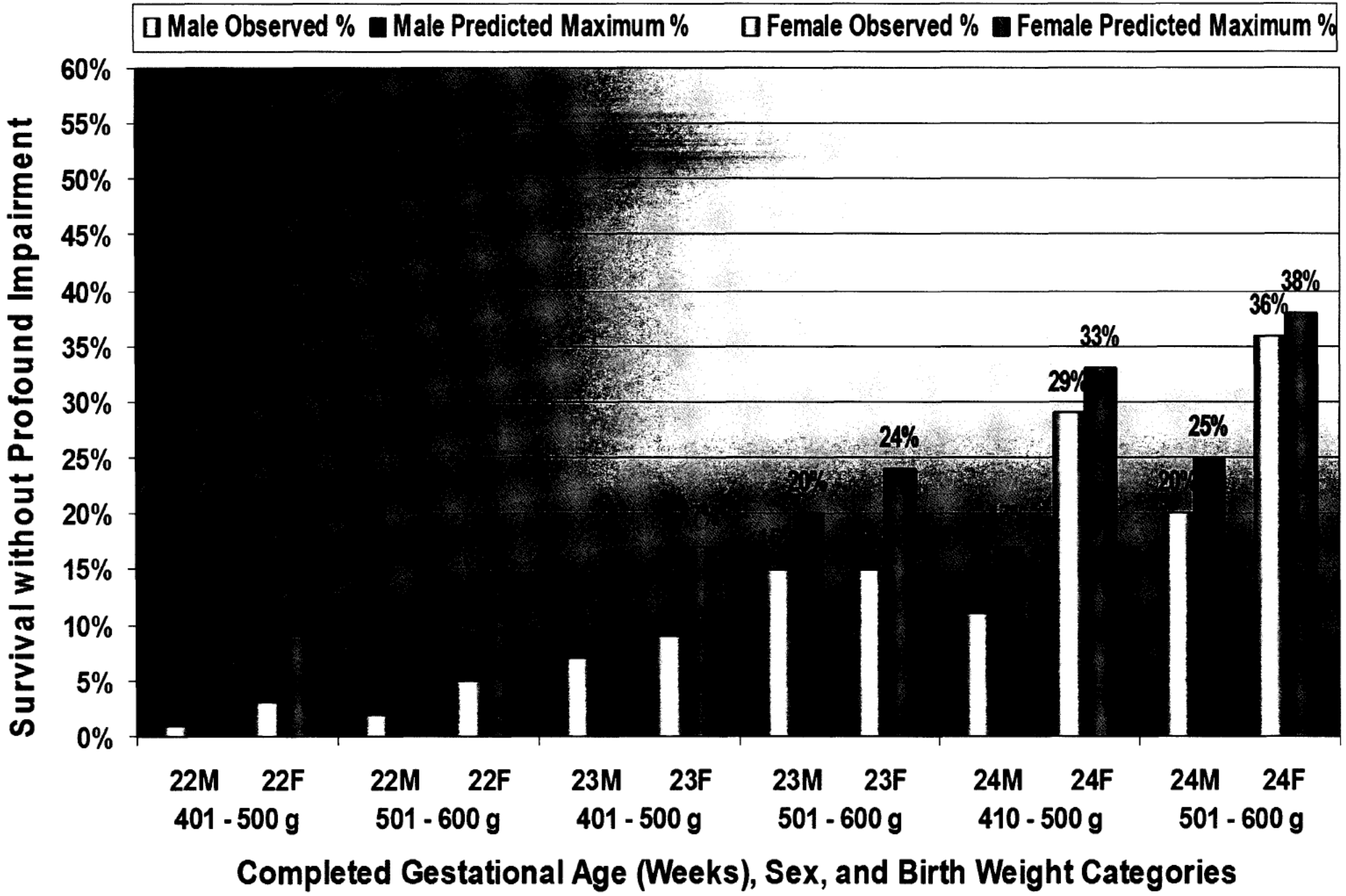


Total Vent. Days & Hospital Days Per Survivor without Profound NDI

	22 wks	23 wks	24 wks	25 wks
Vent Days Males	324	129	81	54
Females	99	103	66	42
Hosp Days Males	610	267	188	153
Females	203	233	158	124

Estimated Benefits and Burdens of Universal rather than Selective Use of NIC for 22-23 Wk Infants

Per 100 infants born at 22-23 wks

- ≤9 extra survivors, at least 3 with profound NDI
- ≥1906 extra hospital days
- ≥$ 6.3 million estimated cost

Need for more better justified and more explicit methods to weigh benefits & burdens

Nevertheless, available data allows advances over use of GA thresholds

Plan to use Network website to facilitate decision making for individual infants within and outside Network

Is Intensive Care Indicated?

Mandatory

Optional

Investigational

Unreasonable

Hospital, community, or national guidelines derived from best available evidence

Withdrawal of intensive care

Are we being ethically inconsistent?

Are we continuing NIC at a lower likelihood of a good outcome than we require to start NIC? If so, is that justified?

Evidence-Based Ethics

Value judgments and disagreement are unavoidable. Yet, thorough and judicious use of the best evidence relevant to the patient's care and prognosis promotes Rx decisions that are progressively:

less arbitrary

better informed

more individualized

more transparent

more broadly acceptable.

Outcome for Network ELBW Infants on Vent. after Specified Periods (Walsh, et al) Preliminary Analyses

Cohort of infants on ventilator for:	% of Cohort Surviving to Discharge	% Cohort Surviving without Impairment at 18-22 Months
≥1 d (n=4752)	75	27
≥7 d (n=3332)	82	31
≥14 d (n=2794)	85	32
≥21 d (n=2206)	87	31
≥28 d (n=1702)	88	29
≥60 d (n=372)	79	16
≥90 d (n= 72)	61	4

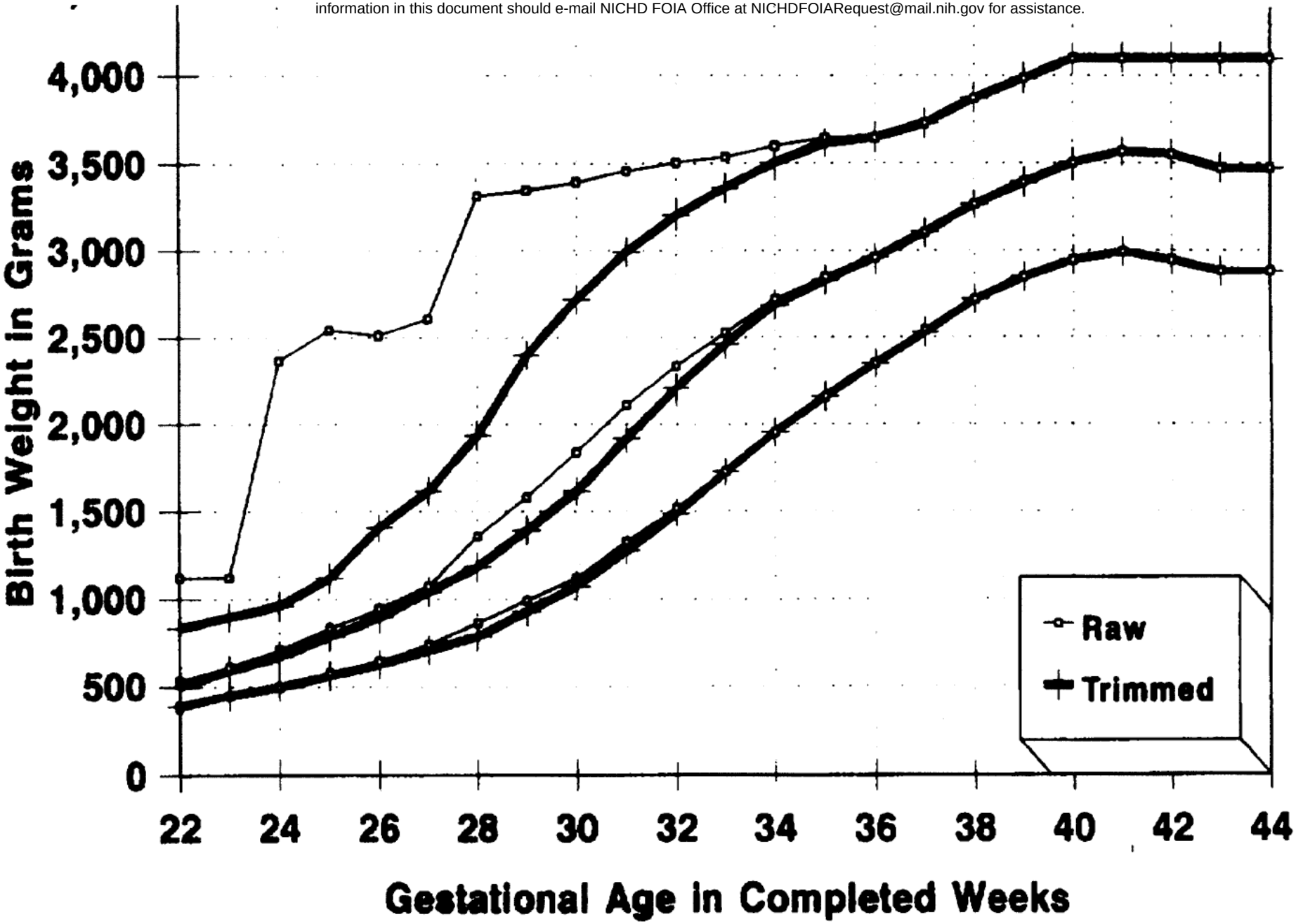
Since the Baby Doe Regulations and the Child Abuse Amendments which now have ambiguous legal standing.

- Increasing court rulings under state law emphasizing parental authority and consideration of quality of life in decisions about care of marginally viable children.

- Other federal laws (e.g., Patient Self Determination Act) to promote autonomy of patients (surrogates).

Law has failed medicine…by creating two conflicting legal standards [state law vs. Federal Child Abuse Amendments]…Physicians must choose which of the two standards to utilize and take their chances.

Frank Clark, MD, JD



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	90th Percentile BW		
	24wks	25wks	26 wks
Kramer et al[1]	790 g	918 g	1060 g
Alexander et al[2]	977 g	1138 g	1362 g

[1] Recent Canadian standard with more sophisticated trimming to produce more plausible means, SDs, & percentiles (Pediatrics 2001; 108:2001)

[2] US standard with statistical trimming of implausible BW for GA (Obstet Gynecol 1996: 87:163)

How many patients are you willing to treat (with MV) if only one has a good outcome (Number Needed to Treat; NNT)?

Highest Acceptable NNT = Threshold NNT*

Excluding costs, threshold NNT = 1/ (AER x RV)

AER = adverse event rate from treatment

RV = relative value (importance) of that adverse event compared to target event prevented by treatment; Expanded formula includes multiple adverse event rates and costs

* Point at which benefits of treating that number of patients equal negative consequences.

Sinclair J et al, J Clin Epidemiol 2001;54:253-261;

Sinclair J. Clin Perinatol 2003;30: 251-268.

Suppose a very high risk group has a 10% rate of survival with MV and 2.5% rate of survival with profound neurodevelopmental impairment (NDI) (adverse event). Do you think MV should be used?

NNT with MV to prevent one death (to gain one survivor) = 10 (NNT with MV to gain one survivor without PNDI = 13)

Threshold NNT = 1/ (AER x RV)

AER = adverse event rate (PNDI) from treatment (MV)

RV = relative value of that adverse event compared to target event prevented by treatment (death). Suppose you consider survival with profound PNDI to be at least 5x times as bad as death.

TNNT (highest acceptable NNT) = 1/(0.025 x 5) = 1/0.125 = 8 (TNNT would be >8 if RV >5)

Even without considering pain caused by NIC or resource costs, NNT/survivor of 10 is too high

If consider suffering, resource use, & costs, NIC may be judged unacceptable or unaffordable at a NNT/survivor ≤ 5

Some persons might be more stringent and require NNT of 5 *per survivor without profound NDI* or *per survivor without moderate-severe NDI*.

Considering the pain, suffering, resource use & cost, what do you think is the maximum number of infants in any risk category who should be given NIC if only one infant benefits?

May express this as maximum number need to treat (NNT) to produce:

- 1 survivor,
- 1 survivor w/o disability
- 1 survivor w/o profound disability?

Your answer(s): _____, _____,&/or _____

Considering the same factors and availability of resources, what do you think is the maximum number of hospital days that can/should be committed to save:

- 1 survivor,
- 1 survivor w/o moderate or severe disability
- 1 survivor w/o profound disability at ≥18 mo.?

Your answer(s):_____,_____, &/or _____

Estimated Benefits/Burdens of Administering Intensive Care to All 501-800 g Infants in Network

Per 100 to Infants 501-800 g BW,

- -Maximum of 8 additional survivors
- -Maximum of 3 extra survivors without CLD (0_2 at 36 wks), NEC. (surgery), or Grade III/IV ICH
- -Maximum of 4 additional survivors without neurodevelopmental impairment (NDI) at 18-22 mo.

Minimum of 985 additional hospital days

How Might Evidence-Based Guidelines Be Developed?

For NICUs with similar outcomes to Network, potential approach based on 1st study & estimated likelihood of survival w/o disability:

- **Investigational (<25%) : SGA girls <550 g; AGA boys <750 g; AGA girls & SGA boys <650 g;.**
- **Optional (25-50%) : SGA girls 550-649 g; AGA boys 750-850 g, AGA girls & SGA boys 650-749 g;**
- **Mandatory (>50%): SGA girls ≥650 g; AGA boys ≥ 850 g. AGA girls & SGA boys ≥750 g; Thresholds lowered 50 g if antenatal steroids given. Might also be lowered 50 g to allow for improved outcomes since study.**

Factors independently related to survival:

- BW
- GA (or SGA)
- Sex
- Antenatal Steroids

Also

- Multiple birth
- C. Section

Singletons: Observed % Survival w/o PNDI

	22 wks	23wks	24wks	25-27 wks
All 401-500 g	2	8	24	26
Male	1	7	11	14
Female	3	9	29	38
All 501-600 g	3	15	28	58
Male	2	15	20	47
Female	4	15	35	66

Observed-Predicted Maximum % Survival w/o PNDI

	22 wks	23wks	24 wks	25-27 wks
All 401-500 g	2 - 15	8 - 17	24 - 28	26 - 28
Male	1 - 12	7 - 12	11 - 15	14 - 17
Female	3 - 18	9 - 20	29 - 33	38 - 39
All 501-600 g	2 - 16	15 - 25	28 - 31	58 - 59
Male	2 - 12	15 - 22	20 - 24	47 - 48
Female	4 - 26	15 - 29	35 - 36	66 - 66

Plausible Maximum % Survival w/o PNDI by Wk GA (At ≥20, NNT ≤5. At 10-20% %, NNT = 5-10)

	22	**23**	**24**	**25-27**
All 401-500 g	8	12	26	27
Male	6	9	**13**	15
Female	**10**	14	**31**	38
All 501-600 g	11	20	29	58
Male	7	18	**22**	47
Female	**15**	**22**	35	66

	Ventilator Days/ Survivor w/o PNDI	Hospital Days/ Survivor w/o PNDI
All 401-500 g	204	406
Male	206	486
Female	140	312
All 501-600 g	155	300
Male	183	387
Female	109	259

Once analyses rechecked, finalized and peer reviewed, plan to place on Network web-site to generate patient-specific estimates of likelihood of good outcome with MV

CONCLUSION

The available data and analyses allows ethical decisions that are considerably more evidence-based, individualized, & transparent than the usual recommendations based solely on GA.

Supplementary slides

Does the law requires require intensive care for all extremely premature infants, regardless of parental wishes?

Advice from one neonatologist:

Focus on what is ethical,
not what is legal!

At least until there is a clear legal standard, try not to think about risk of law suits.

"Dutch doctors change policy on treating preterm babies" (BMJ, June 2001)

In Leiden, "leading center in Holland," NIC will not be recommended before 25 weeks because

- 66% mortality at 23-24 weeks
- 10% of survivors with severe disability, and
- 50% with "serious difficulties in everyday life"

Elsewhere in Holland, NIC is not offered before 26 weeks

EPICure Study

Wood et al, NEJM 2000;343:378.

- Prospective study of 4004 births at 20-25 wk in UK and Ireland during 10 mo of 1995
- Antepartum death rate 70%
- Of live births, 30% died in DR and 43% died before discharge home
- Follow-up at median 30 mo: 49% no disability, 25% severe disability and 23% other disability (unrelated to GA).

Number Needed to Treat (NNT) EPIcure Study

Week	NNT per survivor without any disability	NNT per survivor without severe disability	NNT per survivor
22	20-142	20-142	11-70
23	12-20	7-14	5-9
24	7-8	4-5	3-4
25	4	3	2.5

Severe Disability

Any of the following:

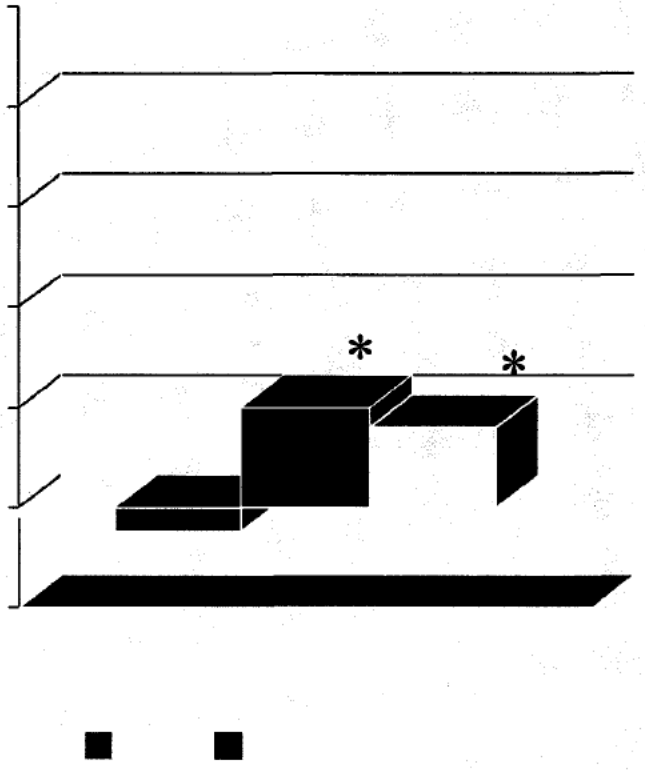
- Bayley<55 ,
- Inability to walk without assistance, sit, use hands to feed self, or support head
- Blind or light perception only
- Impaired hearing uncorrected by hearing aid
- Not communicating or communicating by systematized method only

Survival Without Disability and Number Needed to Treat (NNT)

Wks GA	Total n	% Live Births	% NICU Admits	NNT (assumes no intact survivors without NIC)
22	138	0.7%	5%	20-142
23	241	5%	8%	12.5-20
24	382	12%	15%	6.7-8.3
25	424	23%	27%	3.7-4.3

Quality of Life for "Pat"*

- Blind, deaf, or unable to talk
- Needs equipment, but not help of others, to walk
- Happy, not worried most of the time
- Learns schoolwork very slowly and needs help
- Needs help to eat, bathe, dress, or use toilet
- Sometimes has pain; doesn't interfere



Studies of Saigal et al. (1= perfect health; 0= death)

Preferably developed by professional societies and endorsed at societal level by national ethics organizations or governmental commissions

In their absence, Community guidelines a desirable goal.

Responsibility for application—if not development—within individual centers.

META-ANALYSIS OF ANTENATAL STEROIDS

(Crowley Am J Obstet Gynecol 1995;173:321-34)

	Odds Ratio
Neonatal deaths	0.60
RDS	0.51
Necrotizing enterocolitis	0.35
Periventricular hemorrhage	0.35
Neurologic abnormality (fu)	0.14

NNT per survivor w/o PNDI, Vent. Days, & Hosp. Days

	22 wks	23 wks	24 wks	25-27 wks
All 401-500 g	12-50	8-12	4	4
Male	16-100	11-14	8-9	7
Female	10-33	7-11	3	3
All 501-600 g	9-33	5-7	3-4	2
Male	14-50	5-7	5	2
Female	7-25	5-7	3	1.5
Vent D/ surv, w/o PNDI (female-male)	≥229 99-402	≥ 119 102-135	≥ 88 77-108	≥ 57 48-73
HospD/surv. w/o PNDI (female-male)	≥ 442 204-761	≥ 251 233-269	≥ 200 175-246	≥ 153 135-186

5-02827

NNT per survivor w/o PNDI, Vent. Days, & Hosp. Days

	22 wks	23 wks	24 wks	25-27 wks
All 401-500 g	12-50	8-12	4	4
Male	16-100	11-14	8-9	7
Female	10-33	7-11	3	3
All 501-600 g	9-33	5-7	3-4	2
Male	14-50	5-7	5	2
Female	7-25	5-7	3	1.5
All 401-700g Vent D/ surv, w/o PNDI (female-male)	79-143	95-130	109-129	49-142
All 401-700g Hosp D/ surv, w/o PNDI (female-male)	163-270	217-280	250-295	139-364

NNT & Care Days/Survivor

	22 wks	23 wks	24 wks	25-27 wks	Vent D/ surviv w/o PNDI	Hosp D/ surviv w/o PNDI
All 401-500 g	12-50	8-12	4	4	204	406
Male	16-100	11-14	8-9	7	206	486
Female	10-33	7-11	3	3	140	312
All 501-600 g	9-33	5-7	3-4	2	155	300
Male	14-50	5-7	5	2	183	387
Female	7-25	5-7	3	1.5	109	259

	22 wks	**23 wks**	**24 wks**	**25-27 wks**	Vent D/ surviv w/o PNDI	Hosp D/ surviv w/o PNDI
All 401-500 g	12-50	8-12	4	4	≥204	≥406
Male	16-100	11-14	8-9	7	≥206	≥486
Female	10-33	7-11	3	3	≥140	≥312
All 501-600 g	9-33	5-7	3-4	2	≥155	≥300
Male	14-50	5-7	5	2	≥183	≥387
Female	7-25	5-7	3	1.5	≥109	≥259

In discussing these guidelines with colleagues, these neonatologists emphasize

- Others might select different likelihood thresholds

- BW for mandatory use of IC for AGA infants is ~ 50th percentile at 25 wks for sex-specific BW grids for a large, healthy, recently studied population (Canada)

- Relative to widely quoted guidelines based only on GA, these criteria are less arbitrary, more individualized, and based on large cohorts prospectively assessed through >18 mo. age.

Wishful thinking to assume that babies who are going to die anyway

will usually quickly "declare themselves"

or can be ventilated without much suffering, resource use, and cost

With the staffing & resource limitations in many NICUs, does NIC--particularly prolonged NIC--of the smallest, most immature infants compromise the outcome of larger, more mature infants?

Random error (measurement varies but on average not greater or less than true value) = 0 $\pm$ 2SD

Systematic error (bias) (measurement on average either > or < than true value) = x $\pm$ 2SD

Might there be major systematic error in assessing GA from LMP for extremely premature infants? How would determine?

Benefits vs. Burdens of NIC?

Outcomes Worse Than Early Death?

Compromise of care of outocme infants

Small % have disabilities that many professional or lay persons consider worse than death

Usually <5% of survivors in ELBW FU studies;

Likely to be somewhat higher in smallest infants. In EPICure study (4004 births at 20-25 wk in UK in 1995), 25% of survivors at 30 mo. had profound disability (Bayley<55; inability to walk without assistance, sit, or use hands to feed self, or support head; blind; deaf; or noncommunicative)

Considering pain & suffering to infant, resource limitations, and financial costs*,

what is maximum number of ventilator days justified to salvage one infant without profound NDI?

what is maximum number of hospital days justified to salvage one infant without profound NDI?

Gestational age (wk)
20
25
30
35
40
45
0
10
20
30
40
50
60
70

From:	Zaterka-Baxter, Kristin
To:	Pickett, James; Auman, Jeanette O.; Brinkley, Margo F.; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Das, Abhik; Wade Rich
Subject:	UAB Support Monitoring Letter
Date:	Wednesday, November 22, 2006 10:51:02 AM
Attachments:	Alabama Letter20061122.doc

Hi all,
Just FYI, we sent the attached memo to UAB. This should hopefully cover the bulk of what was discussed on the conference call.
Thanks,
Kris

RTI INTERNATIONAL | **Memorandum**

November 22, 2006

TO: Wally Carlo, MD
Principal Investigator, NICHD NRN
University of Alabama, Birmingham

FROM: Abhik Das, PhD
Principal Investigator, NICHD NRN Data Coordinating Center
RTI, Rockville, MD

SUBJECT: SUPPORT Trial Monitoring Visit

Dear Dr. Carlo,

As you are aware, the Neonatal Research Network Data Coordinating Center at RTI was charged by our Data Safety and Monitoring Committee to conduct on-site monitoring for the SUPPORT trial. Towards this end, we have scheduled a monitoring visit for UAB on December 14 and 15, 2006. The monitoring team will consist of Mr. Wade Rich, who has been brought onboard because of the clinical complexity of this trial and his experience in its design and development, Ms. Kristin Zaterka-Baxter, RTI senior coordinator, and Mr. James Pickett, RTI data manager.

Our monitoring team will arrive for the site visit at 8:30am on Thursday December 14 and leave by 3:00pm on Friday the 15th. We would very much appreciate it if you can have some space available for the full two days for the team to conduct case reviews. A research team member should also be available to answer questions that may arise but will not need to be present during the case review.

The following is the tentative agenda for both days:

December 14

- NICU tour (please schedule this at your convenience and to help us avoid any unnecessary disruption on your unit)

- Case review (please have the following records available):

  - Medical Record Charts
  - Research Charts
  - Completed Case Report Forms
  - Regulatory Binder (if only available for review in your regulatory office, please schedule time at their convenience so we may review the documents)
  - Study Binder (all versions of the study protocol, manual and case report forms)

We will review individual patient records for the following patients:

#	Network ID	Randomization Number	Randomization Date
1	(b) (6)	(b) (6)	(b) (6)
2	(b) (6)		
3	(b) (6)		
4	(b) (6)		
5	(b) (6)		
6	(b) (6)		

The main trial, follow up and all relevant secondary study patient data will be reviewed. In addition to the cases listed above, and if applicable, one active (in house) case will be selected for review. The case will be identified one week prior to the site visit.

December 15

- Continuation of Case Review
- Date Entry Review:
  James Picket will meet with data entry personnel and any other research staff to discuss and review data entry procedures; batch edits; missing forms reports and edit resolutions. Please schedule this review where your data entry takes place. Access to your Network Computer may be necessary to answer any questions about the system. The review will take approximately two hours.
- Summary Discussion:
  Please allow approximately one hour towards the end of the day so the monitoring team can summarize the review and discuss any relevant findings. All research staff are invited to be present, including yourself.

Thank you in advance for helping us assure the quality and accuracy of the Support Trial data. Please feel free to contact me at (301) 770-8214; or adas@rti.org if you have any questions.

Cc. Rosemary Higgins, MD

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Angelita Hensman
Subject: RE: Missing ROP outcomes for SUPPORT
Date: Monday, November 20, 2006 6:39:30 PM

Understood, thanks, AL

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 20, 2006 6:37 PM
To: Abbot Laptook
Cc: Angelita Hensman
Subject: Re: Missing ROP outcomes for SUPPORT

Send the data into RTI when available. For primary trial outcomes, I will likely continue to send reminders (as well as RTI).
When you get my reminder, just let me know the status. Occasionally, we find missing data that were not successfully transmitted, not entered, etc. So for primary outcomes, my reminder is over and above the info that RTI sends to your site. FYI - the PIs have stated that they still want my reminders.
Thanks

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Abbot Laptook <ALaptook@WIHRI.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Angelita Hensman <AHensman@WIHRI.org>
Sent: Mon Nov 20 18:31:27 2006
Subject: RE: Missing ROP outcomes for SUPPORT

Rose
We seem to have more of these than I would like and it reflects that our Opthamologists have long intervals of time between visits once discharged from the NICU. Not sure we can do much about this. We do get these edits from both you and RTI; do we need to respond to both or just one? AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 17, 2006 4:12 PM
To: Abbot Laptook; Angelita Hensman
Cc: Gantz, Marie; Das, Abhik
Subject: Missing ROP outcomes for SUPPORT

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

14

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

14

(b) (6)

Hi

The above infants are missing ROP outcome status for SUPPORT. Can you let us know what the status is?
Thanks for all the effort.

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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higginsr@mail.nih.gov

From: Kristi Watterberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: CONFIDENTIAL STEERING COMMITTEE VOTE
Date: Monday, November 20, 2006 11:43:04 AM

I'm sorry. I was out of town and for some reason this didn't show up on my Treo. So here's your last YES! vote - Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/20/2006 8:16 am >>>
HI,
I have 17 of 18 votes in for this request, all of which are YES votes. The UCSD site will start re-recruiting once we get appropriate arrangements in place.

Thanks to all of you for your prompt responses!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 17, 2006 3:38 PM
To: mcw3@case.edu; Pablo.Sanchez@UTSouthwestern.edu; Shankaran, Seetha; Barbara Stoll; 'Kurt Schibler'; 'Brenda Poindexter'; 'Richard Ehrenkranz'; alaptook@WIHRI.org; 'Krisa Van Meurs'; wacarlo@uab.edu; jon.e.tyson@uth.tmc.edu; goldb008@mc.duke.edu; 'Frantz, Ivan'; 'Bell, Edward'; Roger.Faix@hsc.utah.edu; Kristi Watterberg; Das, Abhik; Michael S Caplan
Subject: CONFIDENTIAL STEERING COMMITTEE VOTE
Importance: High

HI,
At the last Steering committee meeting, the issue of SUPPORT recruitment was raised and it was suggested to bring on additional center(s) to reduce the length of time for the trial. Last month, only 19 patients were randomized. At this rate, it will take 46 months to complete the trial.

We have received permission to add one site, the UCSD center, and Dr. Finer is willing to enroll patients. This will mean that capitation dollars will go to his site for recruitment from the NHLBI co-funding allocation. Please send me a YES /NO vote as soon as you can and preferably by Tuesday, November 21.

Thanks
Rose

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higginsr@mail.nih.gov

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; goldb008@mc.duke.edu; Gantz, Marie
Subject: Re: MISSING ROP OUTCOMES
Date: Monday, November 20, 2006 8:44:33 AM

Certainly. I am in the process of gathering these data.

Kathy J. Auten, MSHS
Project Manager
NICHD Neonatal Research Network Trials
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> wrote on 11/17/2006 04:16:04 PM:

> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
> (b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> 19
>
(b) (6)
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>
> Hi
> The above infants are missing ROP outcome status for SUPPORT. Can
> you let us know what the status is?
> Thanks for all the effort.
> 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: Neil Finer
To: Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: SUPPORT question
Date: Saturday, November 18, 2006 1:22:14 PM

Hi Roger
There will be a few such infants usually in the larger strata. The protocol will require such an infant to receive Surfactant in the DR if randomized to Surf - this would be like an infant receiving prophylactic surf or CPAP if otherwise well, In either case the infant can be weaned immediately to extubation or to DC CPAP. In this case the entire ventilation arm could be completed within 1 hour. The oximeter probes should also be placed.
From the previous NRN data, over 90% of eligible infants were intubated and we realized that a few infants would not have initial distress. Some of these will develop alter issues placing them at risk for BPD and ROP.
You guys are doing a fantastic job. Let me know if you have any other issues
Be well
Neil
-----Original Message-----
From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Friday, November 17, 2006 2:45 PM
To: higginsr@mail.nih.gov; Neil Finer
Subject: SUPPORT question

Hi Neil and Rose! This may seem silly, but an issue recently arose here that gave rise to some controversy, and we would like to seek assurance/clarification in the event a similar circumstance recurs.

If an infant is born between 24 0/7 and 27 6/7 weeks GA and antenatal consent for SUPPORT was obtained, but the infant has minimal/no respiratory distress (such that a similar infant not in the study would not be intubated or receive CPAP), does the child have to be put on CPAP or undergo intubation/surf (depending on which arm the child was randomized to) anyway? I am told that the manual of operations does not specifically address this, but I know what my common sense tells me.

Many thanks for your time, consideration and effort!

Roger

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich
Subject: Re:
Date: Friday, November 17, 2006 5:15:47 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye. 13 (b) (6)

Hi

The above infant is missing ROP outcome status for SUPPORT. Can you let us know what the status is?
Thanks for all the effort.

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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higginsr@mail.nih.gov

Hi Rose, that baby did not intially return for her eye exam She was finally tracked down and brought back for a final exam on September 18 2006. That exam showed fully mature vessels(zone 4, stage 0 bilaterally). That info was recorded on the SUPP10 but has not yet been transmitted. We have a new person doing our data entry and some of our data entry is backed up. It will be sent with our next transmission, sorry for the delay.
Monica

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]; Michael O`Shea
Cc: Gantz, Marie; Das, Abhik
Subject: RE: MISSING ROP OUTCOMES
Date: Friday, November 17, 2006 4:27:23 PM

Our Network computer has been on the blink since the first of the month so we have been unable to enter any data since the end of October. We could not resolve the problem at our site so it was shipped to RTI a few days ago.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 17, 2006 4:17 PM
To: Michael O`Shea; Nancy Peters
Cc: Gantz, Marie; Das, Abhik
Subject: MISSING ROP OUTCOMES

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	20	(b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	20	(b) (6)
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	20	(b) (6)

Hi
The above infants are missing ROP outcome status for SUPPORT. Can you let us know what the status is?
Thanks for all the effort.
Rose

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: MIssing ROP outcomes for SUPPORT
Date: Friday, November 17, 2006 4:10:58 PM

Sure – Ruth is out next week so when she gets back I'm sure she'll fill in the needed forms.
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, November 17, 2006 4:07 PM
To: Duara, Shahnaz; Everett, Ruth
Cc: Gantz, Marie; Das, Abhik
Subject: MIssing ROP outcomes for SUPPORT

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	8	(b) (6) [redacted]
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	8	
50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.	8	
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Hi
The above infants are missing ROP outcome status for SUPPORT. Can you let us know what the status is?
Thanks for all the effort.
Rose

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

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT TRIAL ENROLLMENT
Date: Friday, November 17, 2006 1:16:22 PM

Yes -

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, November 17, 2006 1:14 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: SUPPORT TRIAL ENROLLMENT

Cathy
We had only 19 babies enrolled in SUPPORT last month – at this rate, we have 419 infants and need 1300 – it will take 46 more months. Dorothy Gail from NHLBI was enthusiastic regarding addition of the UCSD site – what do you think – should I get her ok, then a steering committee vote (as funds in essence will be taken from active nrn sites for UCSD)?
Thanks
Rose

Rosemary D. Higgins, M.D.
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From:	Zaterka-Baxter, Kristin
To:	Zaterka-Baxter, Kristin; mcw3@cwru.edu; Nancy Newman; Pablo.Sanchez@UTSouthwestern.edu; Nancy Miller; sshankar@med.wayne.edu; ae5357@wayne.edu; [SCRN] Stoll, Barbara; ellen_hale@oz.ped.emory.edu; Michelle Tidwell; Kurt.Schibler@cchmc.org; CATHY A. GRISBY; bpoindex@iupui.edu; lucmille@iupui.edu; dhwilson@iupui.edu; richard.ehrenkranz@yale.edu; monica.konstantino@yale.edu; alaptook@wihri.org; Angelita Hensman; dstevenson@stanford.edu; Krisa Van Meurs; M. Bethany Ball; wcarlo@peds.uab.edu; Monica Collins; Shirley Cosby; vphillips@peds.uab.edu; jon.e.tyson@uth.tmc.edu; Georgia E McDavid; Frantz, Ivan; Furey, Anne; Bell, Edward; Johnson, Karen; roger.faix@hsc.utah.edu; Karen Osborne; Kristi Watterberg; Conra Backstrom
Cc:	nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wade Rich; Huitema, Carolyn Petrie; Newman, Jamie; Gantz, Marie; Pickett, James; Auman, Jeanette O.; Michelle Tidwell
Subject:	RE: Revised Support Manual and approved forms revisions
Date:	Friday, November 17, 2006 12:04:37 PM
Attachments:	SUPP05SafetyMonitor20061101.doc

Dear all,

My apologies for not sending the final clean copy of the SUPP05 form along with the other forms yesterday. I have attached it here.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Thursday, November 16, 2006 3:34 PM
To: 'M. D. Michele Walsh (mcw3@cwru.edu)'; 'Nancy Newman'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Nancy Miller'; 'M. D. Seetha Shankaran (sshankar@med.wayne.edu)'; 'Rebecca Bara (ae5357@wayne.edu)'; [SCRN] Stoll, Barbara; 'ellen_hale@oz.ped.emory.edu'; 'Michelle Tidwell'; 'Kurt.Schibler@cchmc.org'; 'CATHY A. GRISBY'; 'bpoindex@iupui.edu'; 'lucmille@iupui.edu'; 'dhwilson@iupui.edu'; 'richard.ehrenkranz@yale.edu'; 'Monica Konstantino (monica.konstantino@yale.edu)'; 'M. D. Abbot Laptook (alaptook@wihri.org)'; 'Angelita Hensman'; 'dstevenson@stanford.edu'; 'Krisa Van Meurs'; 'M. Bethany Ball'; 'wcarlo@peds.uab.edu'; 'Monica Collins'; 'Shirley Cosby'; 'Vivien Phillips (vphillips@peds.uab.edu)'; 'jon.e.tyson@uth.tmc.edu'; 'Georgia E McDavid'; 'Frantz, Ivan'; 'Furey, Anne'; 'Bell, Edward'; 'Johnson, Karen'; 'roger.faix@hsc.utah.edu'; 'Karen Osborne'; 'Kristi Watterberg'; 'Conra Backstrom'
Cc: 'nfiner@ucsd.edu'; 'Rosemary (NIH/NICHD) [E] Higgins'; Das, Abhik; 'Wade Rich'; Petrie, Carolyn; Newman, Jamie; Gantz, Marie; Pickett, James; Auman, Jeanette O.
Subject: RE: Revised Support Manual and approved forms revisions

Hi all,

Please find attached the clean copies of the revised Support forms dated November 1, 2006. Please begin using the hard copy forms as soon as possible. The DMS will be updated shortly and we will send you an email notification when the system is available via transmission.

Thanks and please let me know if you have any questions.
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International

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Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

Complete a form each day through DOL 14 **1. Study Day:** _ _ **2. Date:** _ _ / _ _ / _ _ _ _.

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
2. 04 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
3. 06 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
4. 08 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
5. 10 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
6. 12 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
7. 14 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
8. 16 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
9. 18 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
10. 20 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
11. 22 : 00	_ _ : _ _	_._ _ _	___	_._ _ _	___
12. 23 : 59	_ _ : _ _	_._ _ _	___	_._ _ _	___

5. Oximeter Alarm Checks Q6hr/day

a. _ _ : _ _

b. _ _ : _ _

c. _ _ : _ _

d. _ _ : _ _

6. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: _ _ _

4. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 08 : 00	_ _ : _ _	_._ _	_ _ _	_ _ _	_._ _	___	___	_._ _ _	___
2. 16 : 00	_ _ : _ _	_._ _	_ _ _	_ _ _	_._ _	___	___	_._ _ _	___
3. 23 : 59	_ _ : _ _	_._ _	_ _ _	_ _ _	_._ _	___	___	_._ _ _	___

* Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

From:	Zaterka-Baxter, Kristin
To:	mcw3@cwru.edu; Nancy Newman; Pablo.Sanchez@UTSouthwestern.edu; Nancy Miller; sshankar@med.wayne.edu; ae5357@wayne.edu; [SCRN] Stoll, Barbara; ellen_hale@oz.ped.emory.edu; Michelle Tidwell; Kurt.Schibler@cchmc.org; CATHY A. GRISBY; bpoindex@iupui.edu; lucmille@iupui.edu; dhwilson@iupui.edu; richard.ehrenkranz@yale.edu; monica.konstantino@yale.edu; alaptook@wihri.org; Angelita Hensman; dstevenson@stanford.edu; Krisa Van Meurs; M. Bethany Ball; wcarlo@peds.uab.edu; Monica Collins; Shirley Cosby; vphillips@peds.uab.edu; jon.e.tyson@uth.tmc.edu; Georgia E McDavid; Frantz, Ivan; Furey, Anne; Bell, Edward; Johnson, Karen; roger.faix@hsc.utah.edu; Karen Osborne; Kristi Watterberg; Conra Backstrom
Cc:	nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wade Rich; Petrie, Carolyn; Newman, Jamie; Gantz, Marie; Pickett, James; Auman, Jeanette O.
Subject:	RE: Revised Support Manual and approved forms revisions
Date:	Thursday, November 16, 2006 3:33:42 PM
Attachments:	SUPP04NICUAdmission20061101.doc SUPP05ASafetyMonitor20061101.doc SUPP05BOximeterReplacement20061101.doc SUPP06 Prot Dev20061101.doc SUPP08Adverse Event20061101.doc SUPP09OutcomeForm20061106.doc

Hi all,

Please find attached the clean copies of the revised Support forms dated November 1, 2006. Please begin using the hard copy forms as soon as possible. The DMS will be updated shortly and we will send you an email notification when the system is available via transmission.

Thanks and please let me know if you have any questions.
Kris

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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 ≥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
   Complete this question only if Q.B.1 = YES

   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: (Month Day Year)	c) Time: (Hour Min)	d) Type:*
1	__ __/__ __/__ __ __ __	__ __: __ __	—
2	__ __/__ __/__ __ __ __	__ __: __ __	—
3	__ __/__ __/__ __ __ __	__ __: __ __	—
4	__ __/__ __/__ __ __ __	__ __: __ __	—

*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

SAFETY MONITORING FORM (Supplemental Form)

SUPP05A version 4.0
Revised June 5, 2006
Revised November 1, 2006

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Report each time an intubation/extubation occurs after admission to the NICU through DOL 14. Number each event sequentially.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
If yes

a. Record the time of intubation __ __ : __ __ (Hr : Min)

b. Record the following prior to intubation :
1. Were blood gases obtained within 6 hours prior to the event? Y N
If yes,
a. pH __. __ __
b. PCO_2 __ __ __
2. FiO_2 __. __ __
3. Saturation __ __ __
4. Apnea? Y N
5. Sepsis/R/O Sepsis? Y N
6. Hemodynamic instability? Y N
7. Clinically significant PDA? Y N
8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
If Yes,

a. Record the time of extubation __ __ : __ __ (Hr : Min)

b. Type of extubation: ___

1= Planned	2= Accidental

c. Record the following prior to extubation
1. Were blood gases obtained within 6 hours prior to the event? Y N
If yes,
a. pH __. __ __
b. PCO_2 __ __ __
2. FiO_2 __. __ __
3. Saturation __ __ __

Initials of person completing this form: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
If yes

a. Record the time of intubation __ __ : __ __ (Hr : Min)

b. Record the following prior to intubation :
1. Were blood gases obtained within 6 hours prior to the event? Y N
If yes,
a. pH __. __ __
b. PCO_2 __ __ __
2. FiO_2 __. __ __
3. Saturation __ __ __
4. Apnea? Y N
5. Sepsis/R/O Sepsis? Y N
6. Hemodynamic instability? Y N
7. Clinically significant PDA? Y N
8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
If Yes,

a. Record the time of extubation __ __ : __ __ (Hr : Min)

b. Type of extubation: ___

1= Planned	2= Accidental

c. Record the following prior to extubation
1. Were blood gases obtained within 6 hours prior to the event? Y N
If yes,
a. pH __. __ __
b. PCO_2 __ __ __
2. FiO_2 __. __ __
3. Saturation __ __ __

Initials of person completing this form: __ __ __

The Surfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Replacement Oximeter Form

Center: ___ Site: ___ Network No. ___ ___ ___ ___ Birth No. ___ Mother's Initials: ___ ___ ___

Complete this form each time a study oximeter is replaced from study initiation to 36 weeks or status.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
2.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
3.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
4.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
5.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
6.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
7.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
8.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
9.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
10.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___

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.
   11. Infant randomizes to incorrect gestational age group
   12. Postnatal steroids given for BPD/CLD within 21 days of life.
   99. 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: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Adverse Event Form

SUPP08 Rel 2.0
March 10, 2005
Revised November 1, 2006

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __ Report No. __ __

Complete this form for any randomized infant who experienced one or more of the following adverse events during the initial 14 days of life. This form will be keyed at the sites.

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	__ __/__ __/__ __ __ __	___	
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: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

OUTCOME STATUS FORM

SUPP09 Rel 2.1
January 4, 2005
Revised October 26, 2005
Revised November 1, 2006

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 or withdrawn (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	6 = Withdrawn from study

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
2= Betamethasone
3= Hydrocortisone
4= Prednisone
5= Other (Specify)_____

Initials of person completing this form: __ __ __

From:	Zaterka-Baxter, Kristin
To:	mcw3@cwru.edu; Nancy Newman; Pablo.Sanchez@UTSouthwestern.edu; Nancy Miller; sshankar@med.wayne.edu; ae5357@wayne.edu; [SCRN] Stoll, Barbara; ellen_hale@oz.ped.emory.edu; Michelle Tidwell; Kurt.Schibler@cchmc.org; CATHY A. GRISBY; bpoindex@iupui.edu; lucmille@iupui.edu; dhwilson@iupui.edu; richard.ehrenkranz@yale.edu; monica.konstantino@yale.edu; alaptook@wihri.org; Angelita Hensman; dstevenson@stanford.edu; Krisa Van Meurs; M. Bethany Ball; wcarlo@peds.uab.edu; Monica Collins; Shirley Cosby; vphillips@peds.uab.edu; jon.e.tyson@uth.tmc.edu; Georgia E McDavid; Frantz, Ivan; Furey, Anne; Bell, Edward; Johnson, Karen; roger.faix@hsc.utah.edu; Karen Osborne; Kristi Watterberg; Conra Backstrom
Cc:	nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wade Rich; Petrie, Carolyn; Newman, Jamie; Gantz, Marie; Price, Jeffrey M.
Subject:	FW: Revised Support Manual and approved forms revisions
Date:	Thursday, November 16, 2006 2:00:03 PM
Attachments:	SUP10.doc SUPPORT_Manual[uc]20061101.doc SUPPORT_Manual[cc]20061101.doc SUPP04NICUAdmission[uc]20061101.doc SUPP05SafetyMonitor[uc]20061101.doc SUPP05ASafetyMonitor[uc]20061101.doc SUPP05BOximeterReplacement[uc]20061101.doc SUPP06 Prot Dev][uc]20061101.doc SUPP08Adverse Event[uc]20061101.doc SUPP09OutcomeForm[uc]20061106.doc

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Hi all,

Please find attached technical memo #10 and the final Support forms revisions with corresponding manual revision dated November 1, 2006. Please note I've included highlighted copies of the forms and both the highlighted and clean version of the manual to help facilitate IRB submission if both forms and the manual are required. Additionally, the newly created from Supp12 has been renumbered to Supp05B for easier flow in the manual. In the next email to come, I will attach a clean version of the forms.

Thanks and please let me know if you have any questions.
Kris

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RTI INTERNATIONAL | **Memorandum**

November 9, 2006

SUPPORT TECHNICAL MEMO # 10

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Manual of Procedures and Forms revisions (SUPP04, 05, 05A, 05B (new), 06. 08 and 09). Version Date November 1, 2006.

Please find below an outline of revisions made to the Manual (version date 11/01/06). All corresponding revised forms are enclosed. Please note all added text appears red and underlined and all ~~deleted~~ text appears red and stricken through.

Chapter 1, Overview and Trial Design, Forms descriptions (page 1-3 and 1- 4)

Safety Monitoring Form (SUPP05A)
This form is to be completed each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Safety Monitoring Form (SUPP05A)
This form is to be completed each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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~~.

Outcome Status Form (SUPP09)
This form will be completed when the infant is discharged home, transferred, if hospitalized at 120 days, ~~or~~ death or withdrawn (whichever comes first).

Chapter 9, Admission to NICU, SUPP04 (page 9-2)

Q.B.2
2. Was a blood gas done within 30 minutes prior to intubation?
Note: Complete this question only if question B.1 = YES

Chapter 10, Safety Monitoring, Form SUPP05, 05A and 05B

SUPP05 (page 10-1)

Q.3

3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.

~~10.2.1 Section A. Blood gas results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59. If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.~~

~~*Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.*~~

Q.3.b

b. Time Measured

~~For blood gas information~~ rRecord the actual time that the FiO2 was obtained ~~blood samples were collected~~ based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

Q.3.f (page 10-2)

f. FiO_2

Record the FiO_2 at the ~~time the blood gas was collected or at other~~ scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

Q.3.h

h. Mode of Support

Record the respiratory support as:

9= No Support all day and off Study oximeter

Q.4

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

Q.4.a

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

Q.4.b

b. Time Measured

~~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.~~

~~For all other time points enter the FiO_2 and Mode of Support.~~

Q.4.f (page 10-3)

f. FiO_2

Record the FiO_2 corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

Q.4.h

h. Mode of Support

9= No Support all day and off Study oximeter

Old Supp05 Q.14 (a new form has been created to capture replacement oximeters SUPP05B)

~~**14 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***~~

Old Supp05 Q.15 changes to Q.6

~~15~~ 6. Was the infant intubated or extubated on this day?

If Yes, Complete ~~Section B and/or Section C of~~ the SUPP05A

SUPP05A, (page 10-4)

DCC Note: since section B and/or C have been removed from the form, the primary change in this section is the renumbering of the form questions. One question has been added regarding blood gases prior to intubation/extubation in two sections of the form and in the manual

Old Section 10.2.2, Section B

10.3 ~~**2.2 Section B**~~. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question ~~15~~ 6 on the SUPP05 is coded "Yes". If more than one intubation/extubation occurs complete a new report ~~Section B~~ for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number

Consecutively number each event as reported on ~~Section B of~~ the SUPP05a form.

Q.3.b.1(intubation) and the same question for Q.4.c.1 (extubation)

1. Were blood gases obtained within 6 hours prior to the event?

~~*Record*~~ *Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.* ~~*, record "*"*~~

SUPP05B (page 10-5)

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. **Episode Number**
Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. **Date Oximeter Replaced**
Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. **Time Oximeter Replaced**
Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. **Replacement Oximeter Serial Number**
Record the six digit serial number of the replacement oximeter used.

e. **Replacement Oximeter Color Code**
Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

Chapter 11, Protocol Deviation, Form SUPP06, page 11-1

Q.2 (option 11, 12 and other code)
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
~~10~~99= Other: Specify type of protocol deviation

Chapter 13, Serious Adverse Experience, Form SUPP08 (page 13-1)

Q.1
~~**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.**~~ Record a consecutive Report Number in the header for each form submitted. This form should be completed and keyed at the sites as soon as possible.

1. Air leak ~~in the first 14 days~~

Chapter 14, Outcome Status, From SUPP09 (page 14-1)

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 or withdrawn (which ever comes first).

DCC Note: this status code has been added:

- **Withdrawn form study**
  Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

Cc Rosemary Higgins, MD

Enclosed: Forms SUPP04, SUPP05, SUPP05A, SUPP05B, SUPP06, SUPP08, SUPP09, Manual of Procedures (highlighted revisions and clean copy)

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006
Revised November 1, 2006

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 each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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 or withdrawn (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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, 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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. Any subsequent extubations will also follow standard practice.

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. $pC0_2$:

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 $Sa0_2$ ≥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?
Note: Complete this question only if question B.1 = YES

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
SUPP05 SUPP05A SUPP05B

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

1. Study Day: Enter the day this form is being completed.
2. Date: Enter the date that corresponds to the Study Day.
3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.
~~10.2.1 Section A. Blood gas results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**~~

~~*Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.*~~

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

~~For blood gas information~~ ~~r~~Record the actual time that the FiO2 was obtained ~~blood samples were collected~~ based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

f. FiO_2
Record the FiO_2 at the ~~time the blood gas was collected or at other~~ scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

4j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. ~~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.~~
~~For all other time points enter the FiO_2 and Mode of Support.~~

c. pH
Record the acid base status of the blood.

d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

g. Source:
Record the source of the blood gas
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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

~~13~~ 5 Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine. The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

~~**14 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~~

~~15~~ 6. Was the infant intubated or extubated on this day?
If Yes, Complete ~~Section B and/or Section C of~~ the SUPP05A

10.3 ~~2.2 Section B~~. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question ~~15~~ 6 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete a new report ~~Section B~~ for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on ~~Section B of~~ the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

~~**Section B**~~
~~1.~~3 Was the infant intubated on this day?
Record Yes if the infant was intubated on this day.
If Yes,
a. ~~If Yes~~, Record the time of intubation:
b. Record the following information prior to intubation:

1. Were blood gases obtained within 6 hours prior to the event?
~~Record~~ Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event. ~~, record ""~~*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
~~2.~~ b. PCO_2

~~3~~2. FiO_2
~~4~~3. Saturation
~~5~~4. Apnea? Record Yes if the infant had Apnea on this day.
~~6~~5. Sepsis/R/O Sepsis? Record Yes if the infant had Sepsis/R./O Sepsis on this day.
~~7~~6. Hemodynamic instability? Record Yes if the infant had hemodynamic instability on this day.
~~8~~7. Clinically significant PDA? Record Yes if the infant had clinically significant PDA on this day.
~~9~~8. Other (specify). Record Yes if the infant had other conditions this day. Specify these.

~~2~~4. Was the infant extubated on this day?

Record Yes if the infant was extubated on this day.

If Yes,

a. ~~If Yes,~~ Record the time of intubation:

b. Type of extubation:
   1= Planned
   2= Accidental

c. Record the following prior to extubation

1. Were blood gases obtained within 6 hours prior to the event?

~~Record~~ Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event. ~~; record ""~~*

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:

~~1~~a. pH

~~2~~b. PCO_2

~~3~~2. FiO_2

~~4~~3. Saturation

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. Episode Number

Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. Date Oximeter Replaced

Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. Time Oximeter Replaced

Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. Replacement Oximeter Serial Number

Record the six digit serial number of the replacement oximeter used.

e. Replacement Oximeter Color Code

Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

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.
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
~~10~~99= 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.**~~ Record a consecutive Report Number in the header for each form submitted. 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 Kris Zaterka-Baxter 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, ~~of~~ death or withdrawn (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.

- **Withdrawn form study**
  Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

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 or 4b is a partial retinal detachment
- Code 5 = stage 5 which is a total retinal detachment
- Code 6 = Post laser/cyro (do not use stages)
- Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations
  (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time-during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b)

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

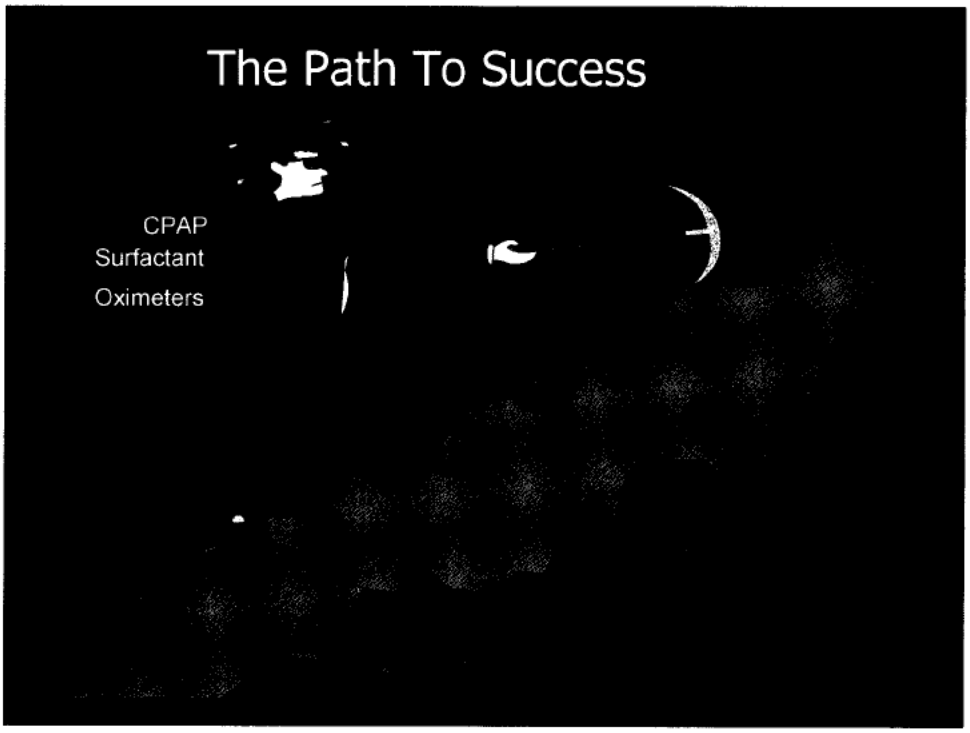
Signature of person explaining and getting consent DATE

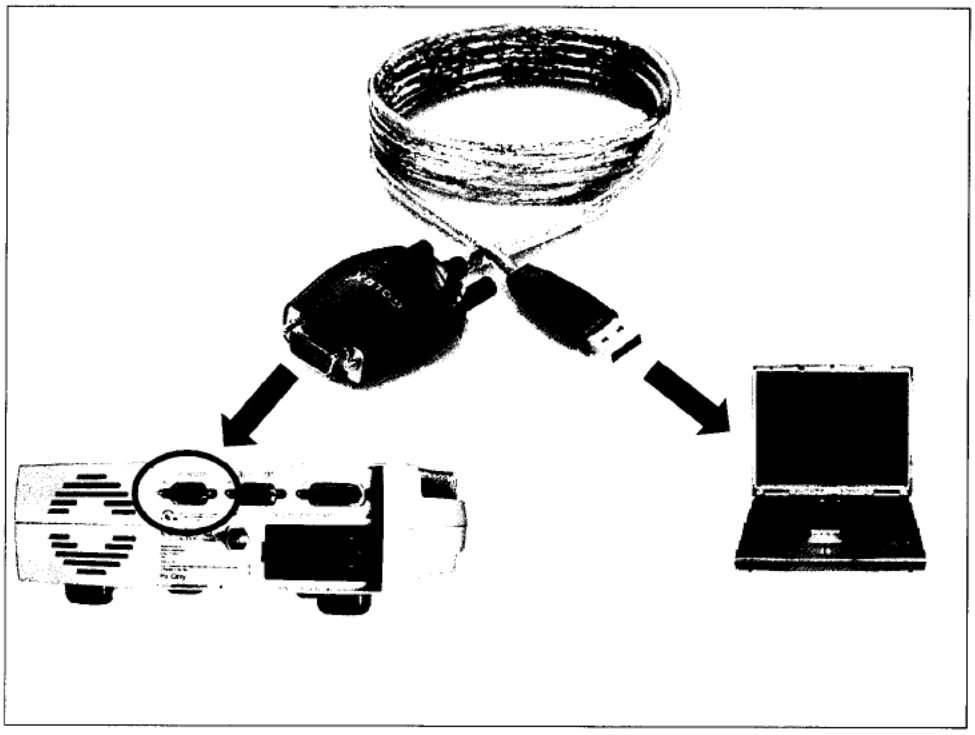
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

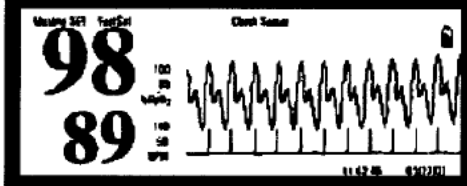
Use arrow key to select "Binary".

Select button.

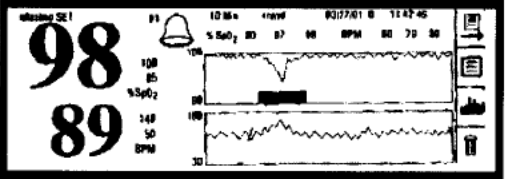
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

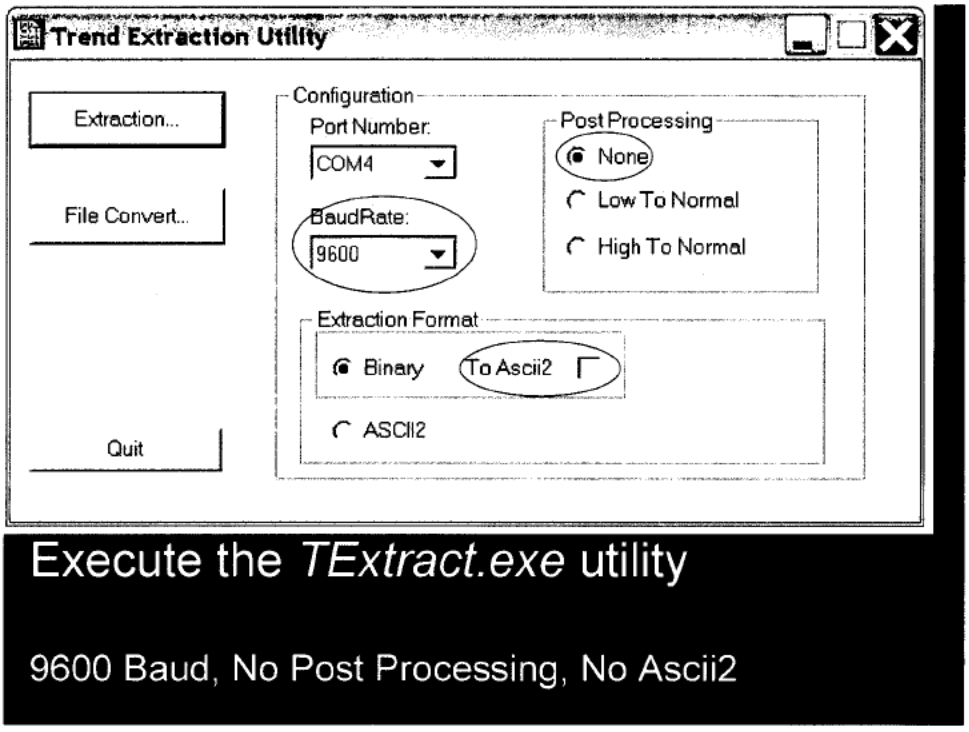
Make sure the Radical is in run mode and not in mode.



YES

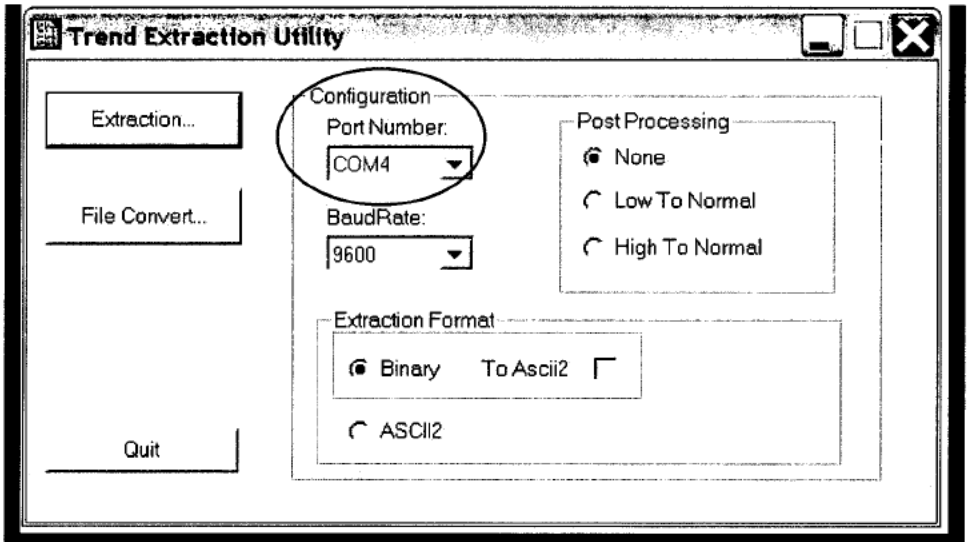


No

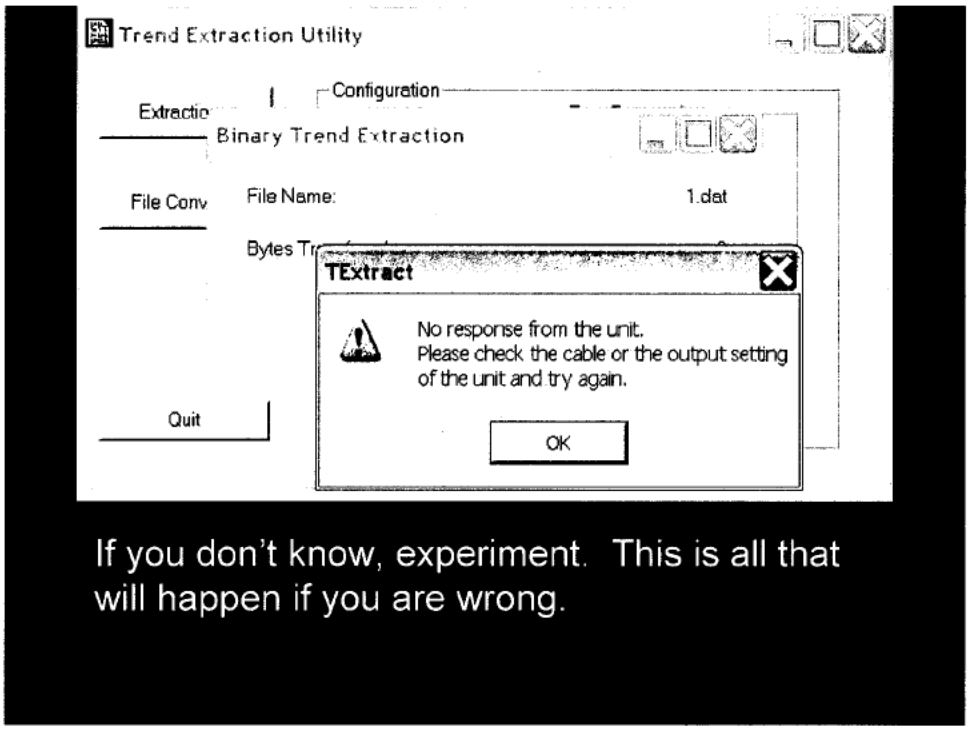


Execute the *TExtract.exe* utility

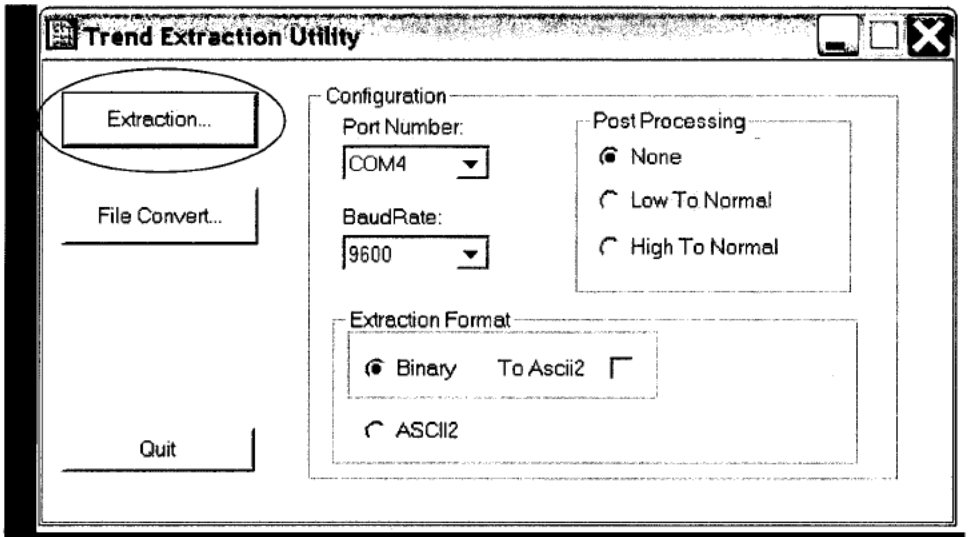
9600 Baud, No Post Processing, No Ascii2



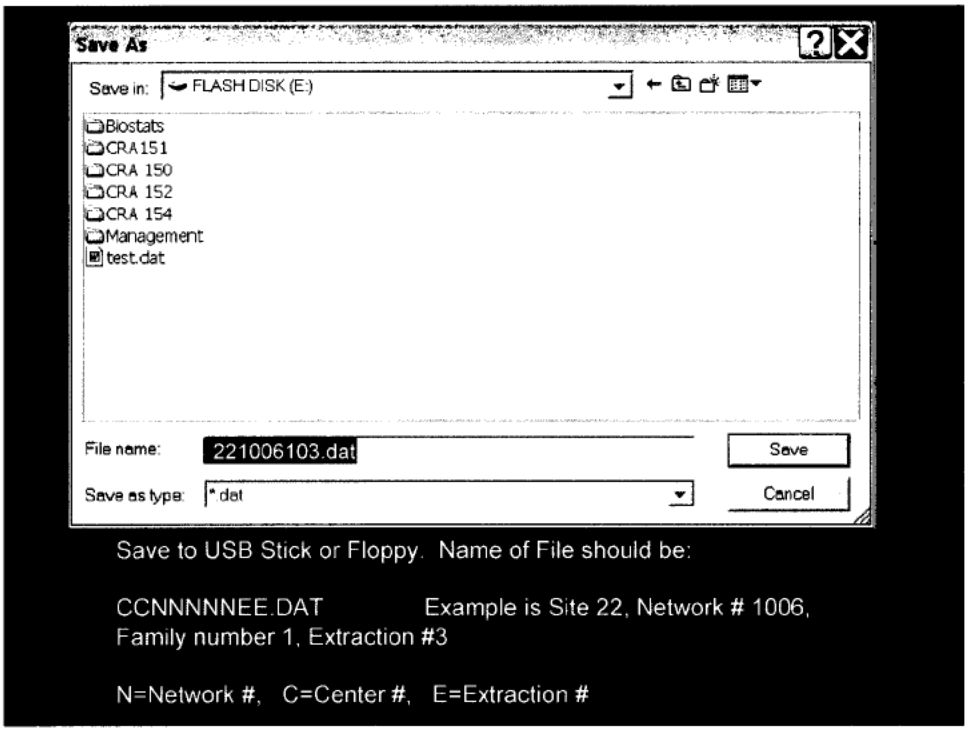
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.



If you don't know, experiment. This is all that will happen if you are wrong.



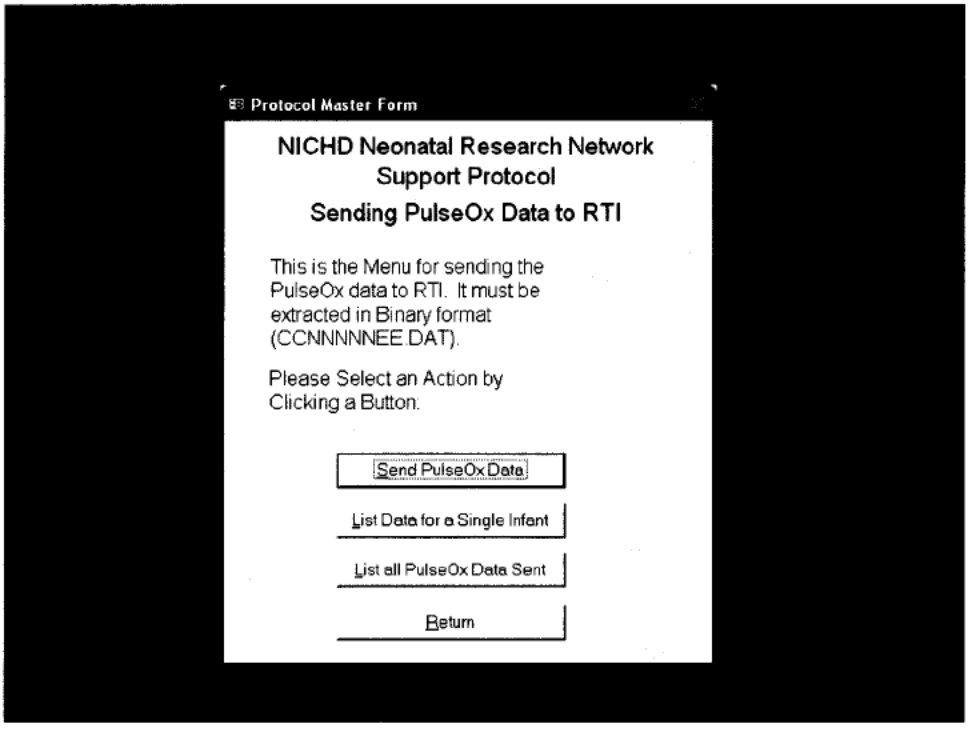
Hit Extraction.

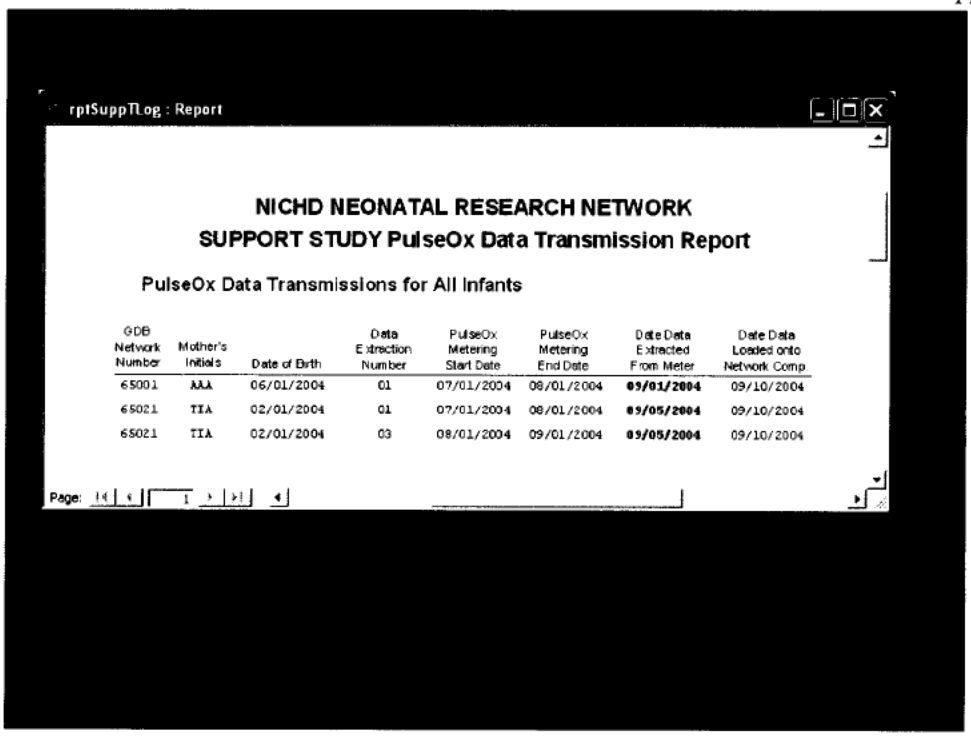


Save to USB Stick or Floppy. Name of File should be:

CCNNNNNEE.DAT Example is Site 22, Network # 1006, Family number 1, Extraction #3

N=Network #, C=Center #, E=Extraction #





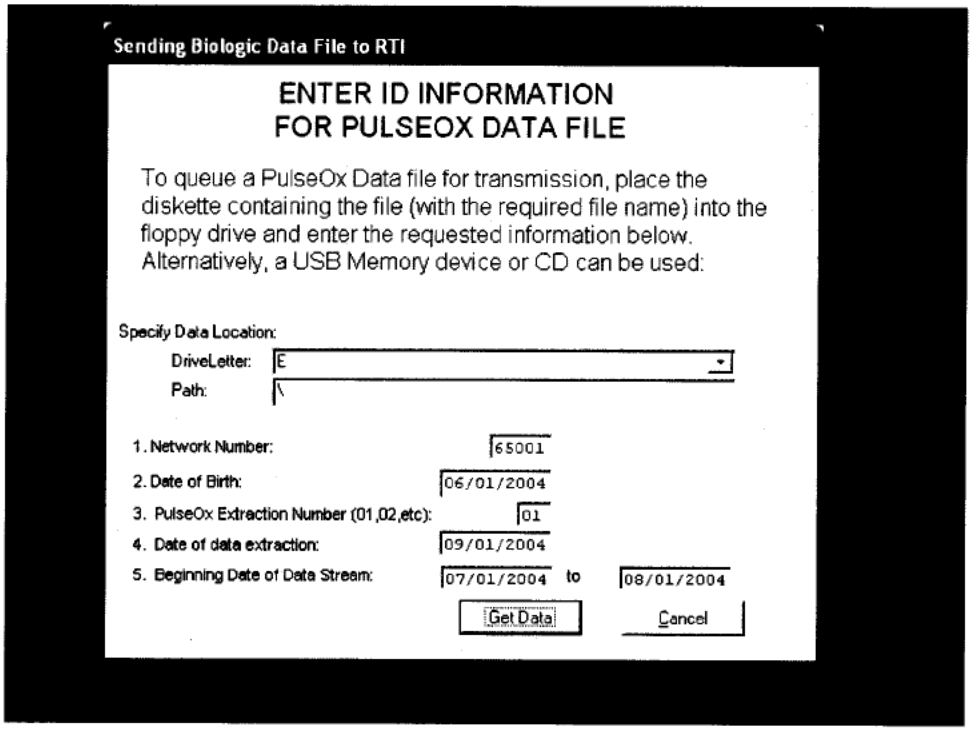
rptSuppTLog : Report

NICHD NEONATAL RESEARCH NETWORK
SUPPORT STUDY PulseOx Data Transmission Report

PulseOx Data Transmissions for All Infants

GDB Network Number	Mother's Initials	Date of Birth	Data Extraction Number	PulseOx Metering Start Date	PulseOx Metering End Date	Date Data Extracted From Meter	Date Data Loaded onto Network Comp
65001	AAA	06/01/2004	01	07/01/2004	08/01/2004	**09/01/2004**	09/10/2004
65021	TIA	02/01/2004	01	07/01/2004	08/01/2004	**09/05/2004**	09/10/2004
65021	TIA	02/01/2004	03	08/01/2004	09/01/2004	**09/05/2004**	09/10/2004

Page: 1



Sending Biologic Data File to RTI

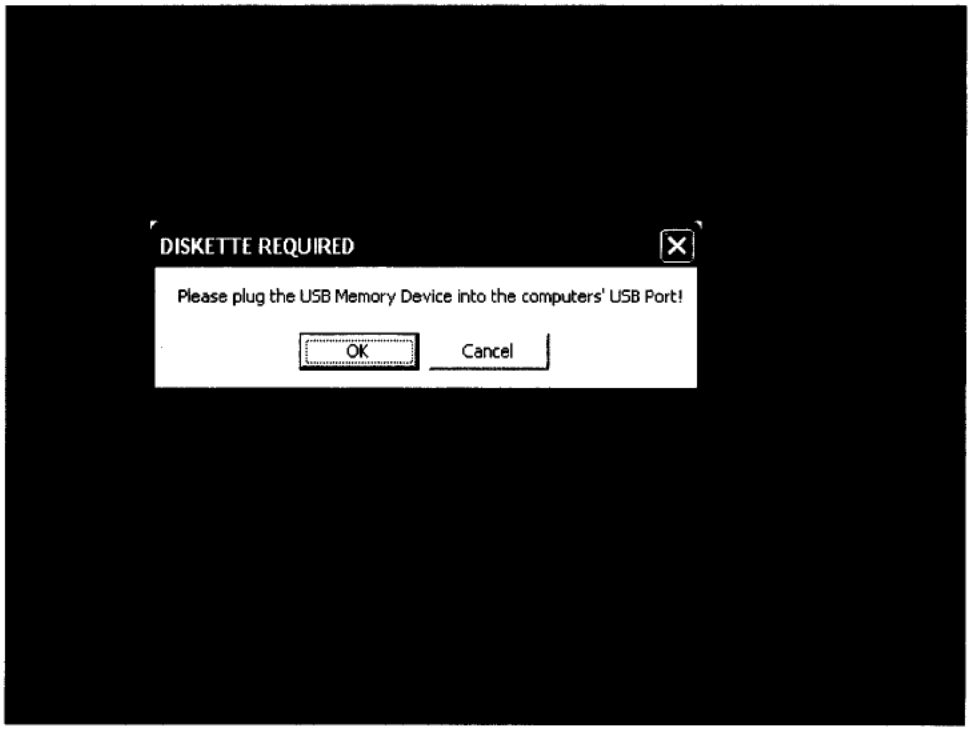
ENTER ID INFORMATION FOR PULSEOX DATA FILE

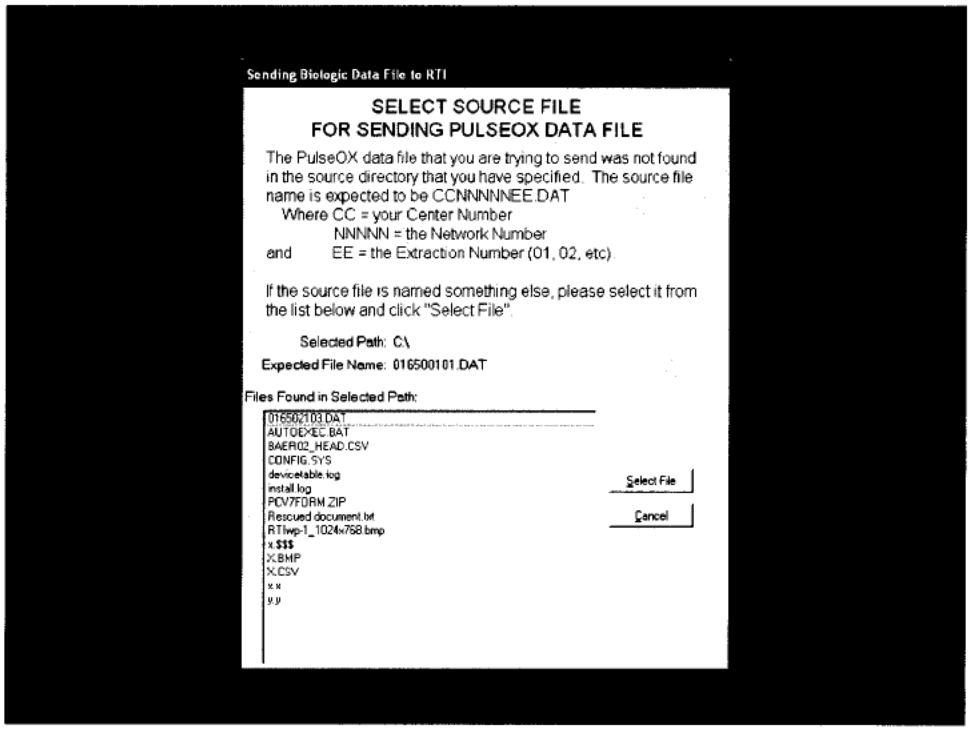
To queue a PulseOx Data file for transmission, place the diskette containing the file (with the required file name) into the floppy drive and enter the requested information below. Alternatively, a USB Memory device or CD can be used:

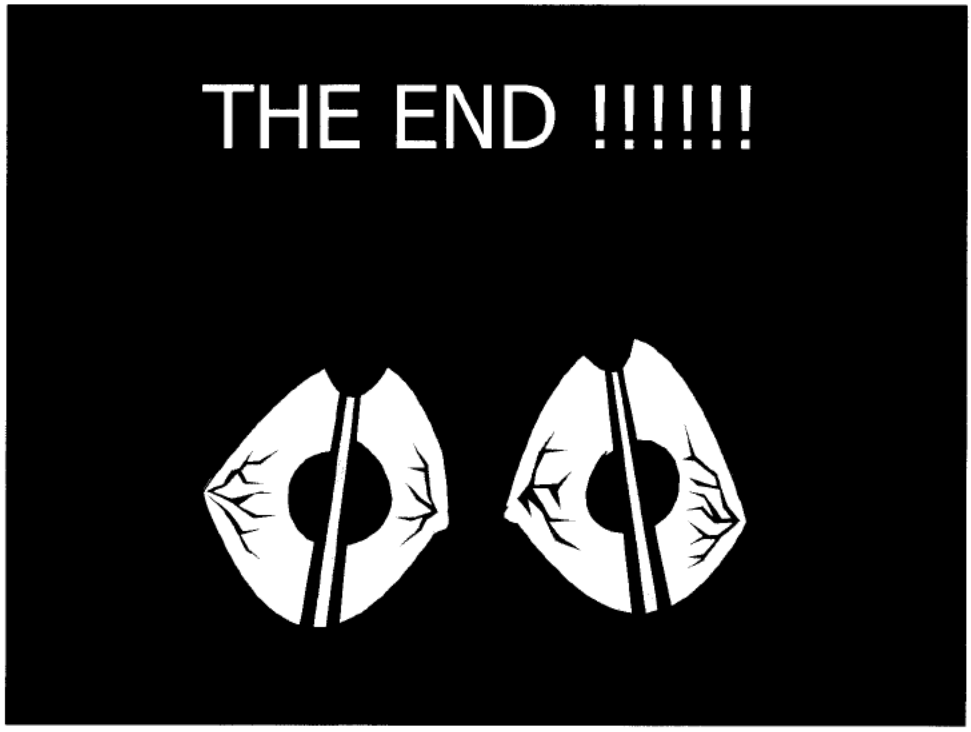
Specify Data Location:
DriveLetter: E
Path: \

1. Network Number: 65001
2. Date of Birth: 06/01/2004
3. PulseOx Extraction Number (01,02,etc): 01
4. Date of data extraction: 09/01/2004
5. Beginning Date of Data Stream: 07/01/2004 to 08/01/2004

Get Data Cancel







APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

 # xxxx

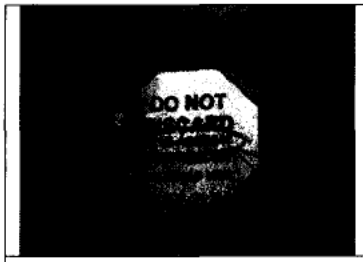
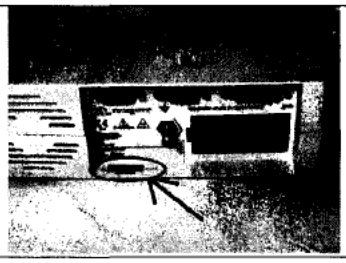
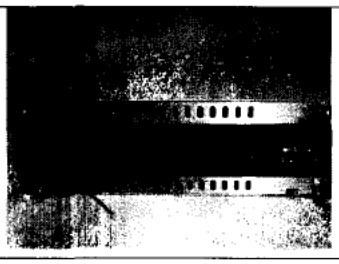
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
     (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
   Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006
Revised November 1, 2006

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 each time an intubation/extubation occurs after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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.

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, death or withdrawn (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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, 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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. Any subsequent extubations will also follow standard practice.

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 $Sa0_2$ ≥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?

Note: Complete this question only if question B.1 = YES

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
SUPP05 SUPP05A SUPP05B

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

1. Study Day: Enter the day this form is being completed.

2. Date: Enter the date that corresponds to the Study Day.

3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured
Record the actual time that the FiO2 was obtained based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

f. FiO_2
Record the FiO_2 at the scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one.

c. pH
Record the acid base status of the blood.
d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

g. Source:
Record the source of the blood gas
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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

5. Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine. The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

6. Was the infant intubated or extubated on this day?
If Yes, Complete the SUPP05A

10.3 Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 6 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete a new report for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

3 Was the infant intubated on this day?
Record Yes if the infant was intubated on this day.
If Yes,
a. Record the time of intubation:
b. Record the following information prior to intubation:

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation
4. Apnea? Record Yes if the infant had Apnea on this day.
5. Sepsis/R/O Sepsis? Record Yes if the infant had Sepsis/R./O Sepsis on this day.
6. Hemodynamic instability? Record Yes if the infant had hemodynamic instability on this day.
7. Clinically significant PDA? Record Yes if the infant had clinically significant PDA on this day.
8. Other (specify). Record Yes if the infant had other conditions this day. Specify these.

4. Was the infant extubated on this day?
Record Yes if the infant was extubated on this day.

If Yes,
a. Record the time of intubation:

b. Type of extubation:
1= Planned
2= Accidental

c. Record the following prior to extubation

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. Episode Number
Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. Date Oximeter Replaced
Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. Time Oximeter Replaced
Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. Replacement Oximeter Serial Number
Record the six digit serial number of the replacement oximeter used.

e. Replacement Oximeter Color Code
Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

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.
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
99= 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:**

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 Record a consecutive Report Number in the header for each form submitted. This form should be completed and keyed at the sites as soon as possible.

1. Air leak
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 Kris Zaterka-Baxter 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, death or withdrawn (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.

   - **Withdrawn form study**
     Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations
  (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b) [redacted]

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the → button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

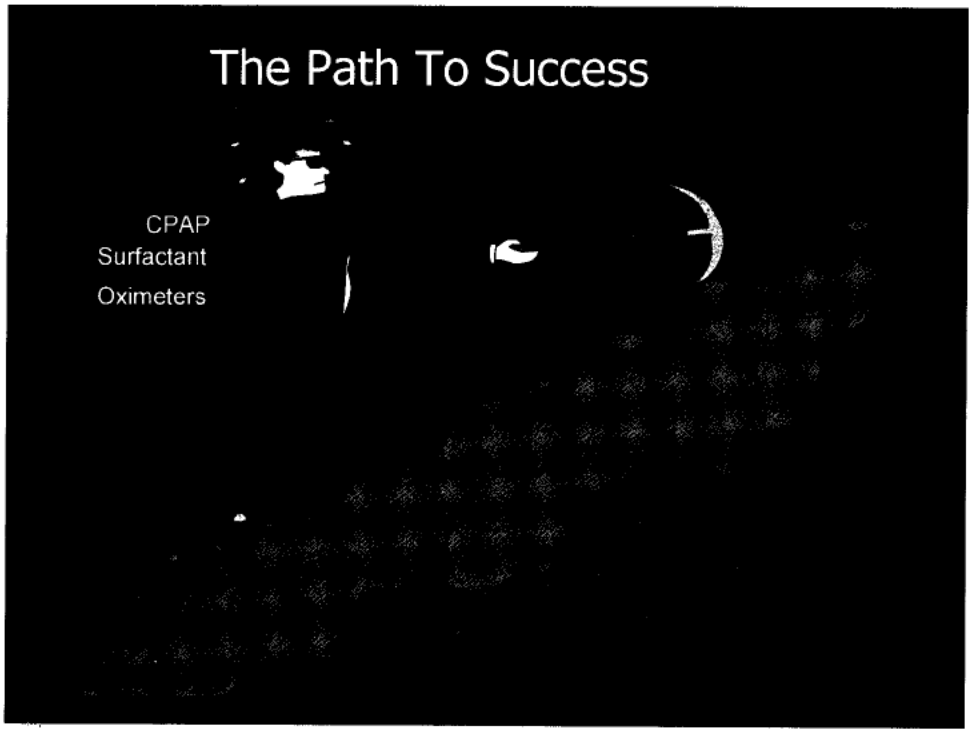
Signature of person explaining and getting consent DATE

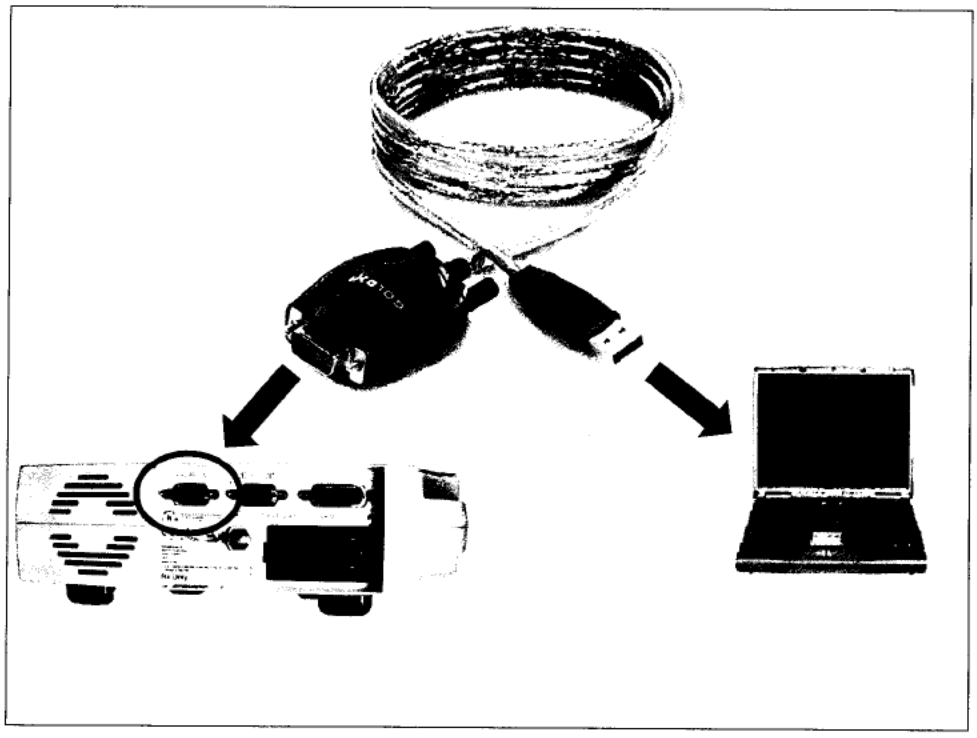
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

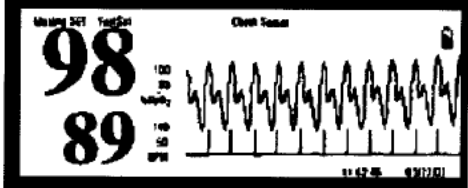
Use arrow key to select "Binary".

Select button.

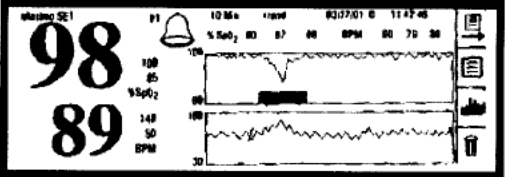
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

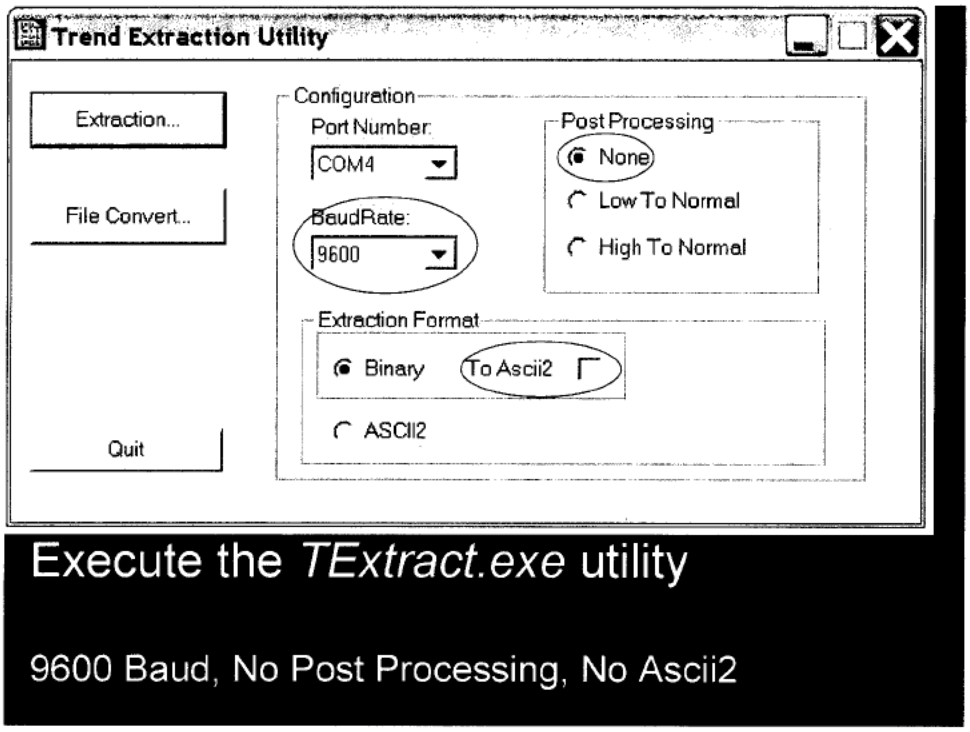
Make sure the Radical is in run mode and not in mode.



YES

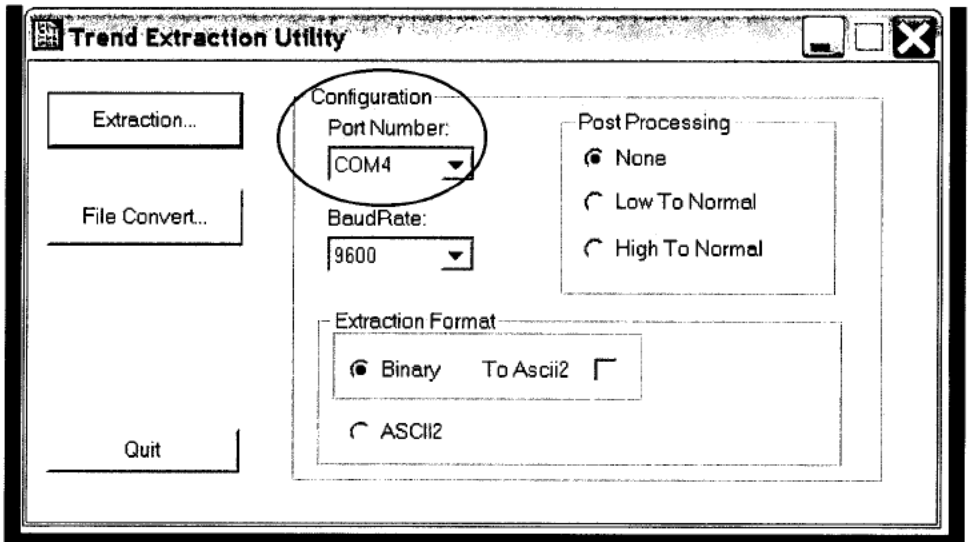


No

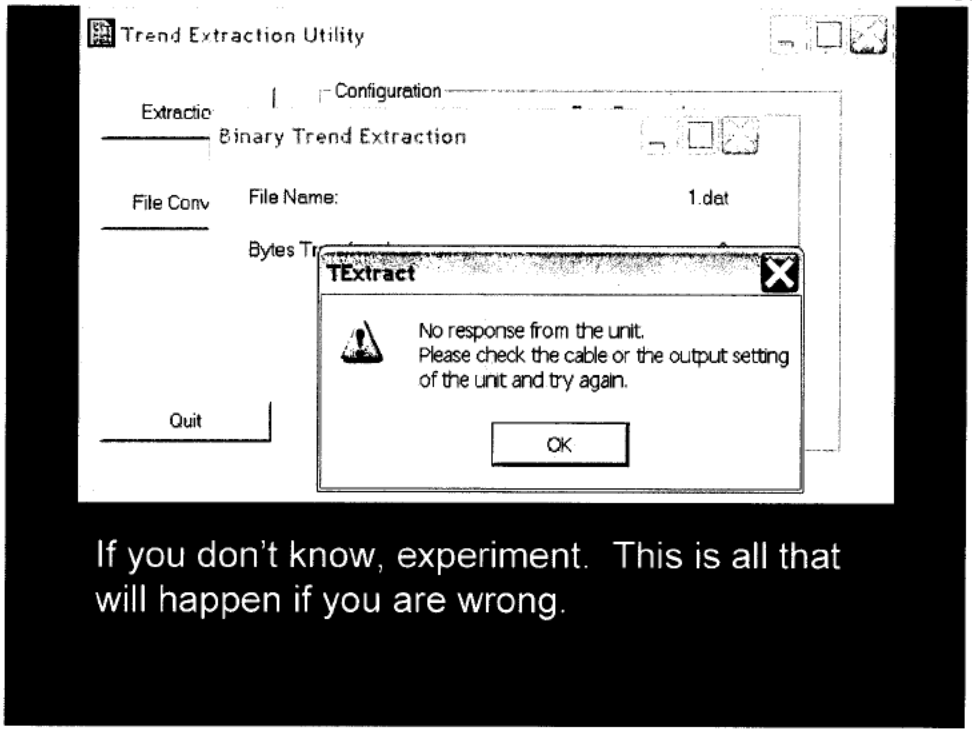


Execute the *TExtract.exe* utility

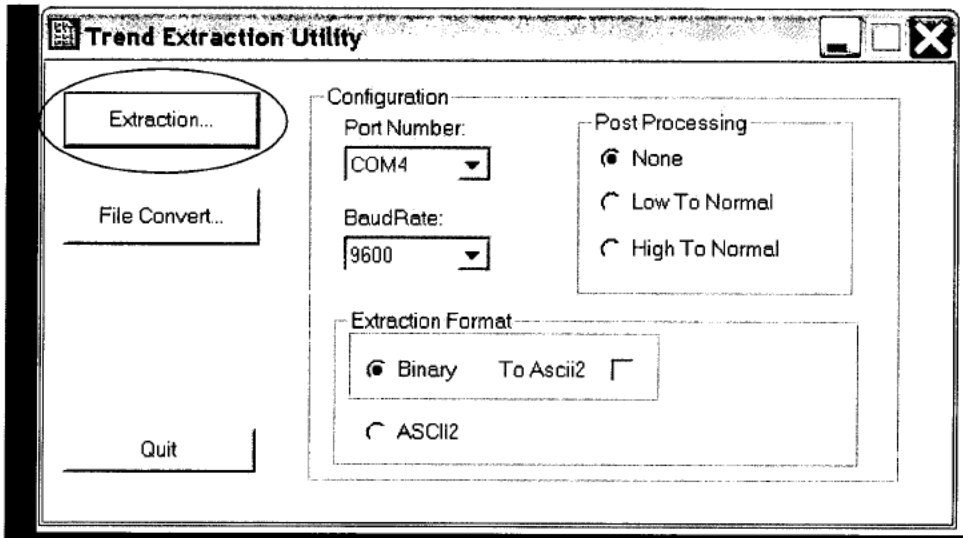
9600 Baud, No Post Processing, No Ascii2



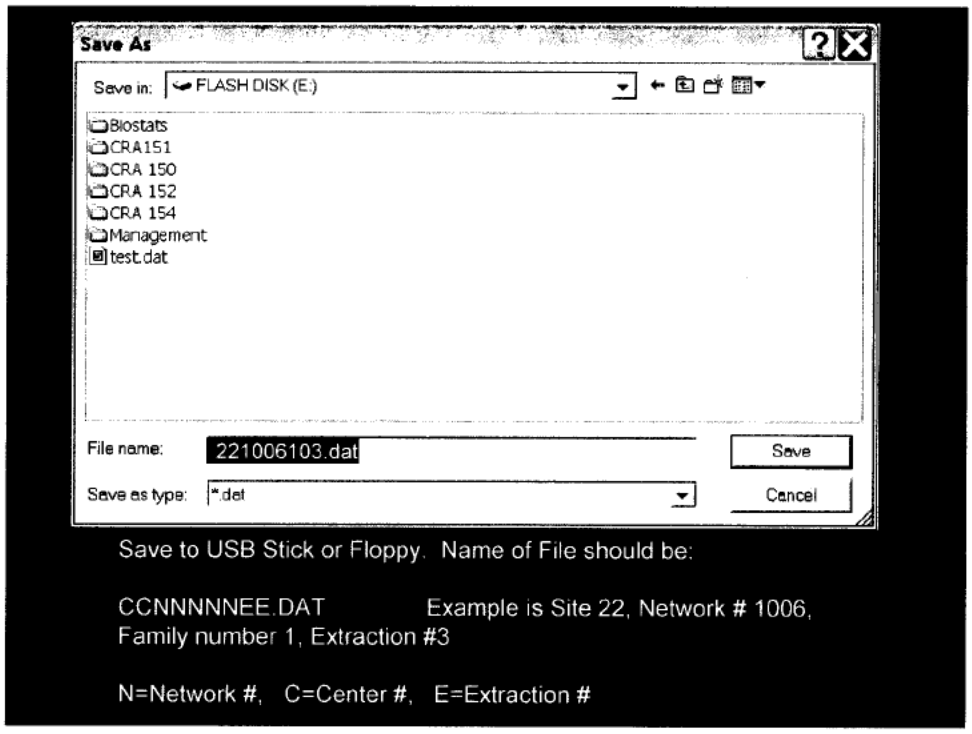
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

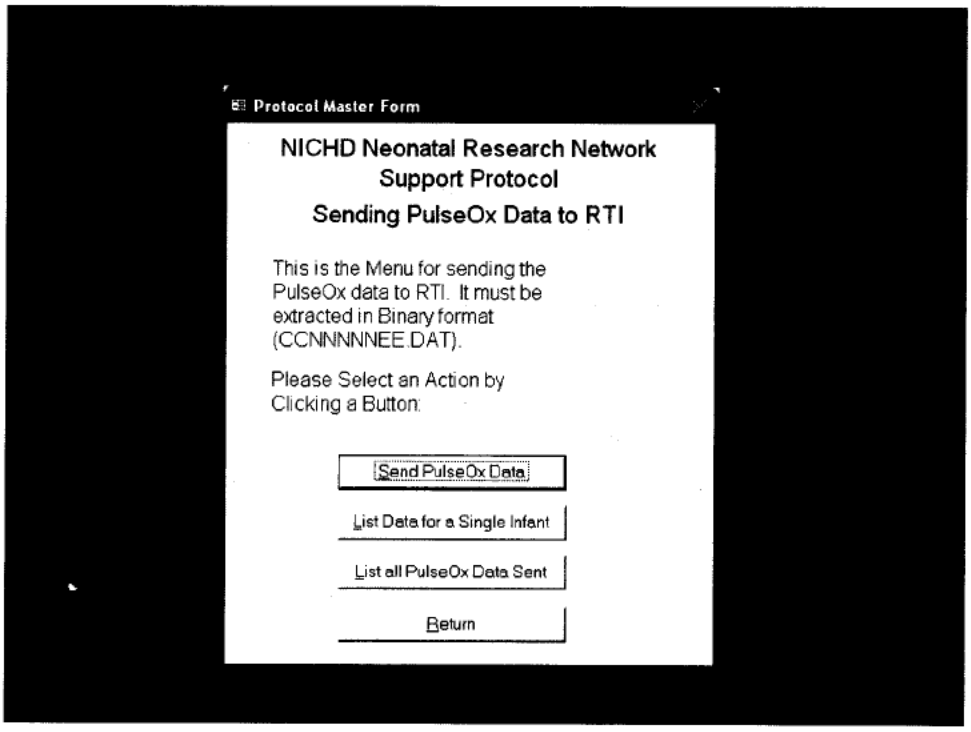


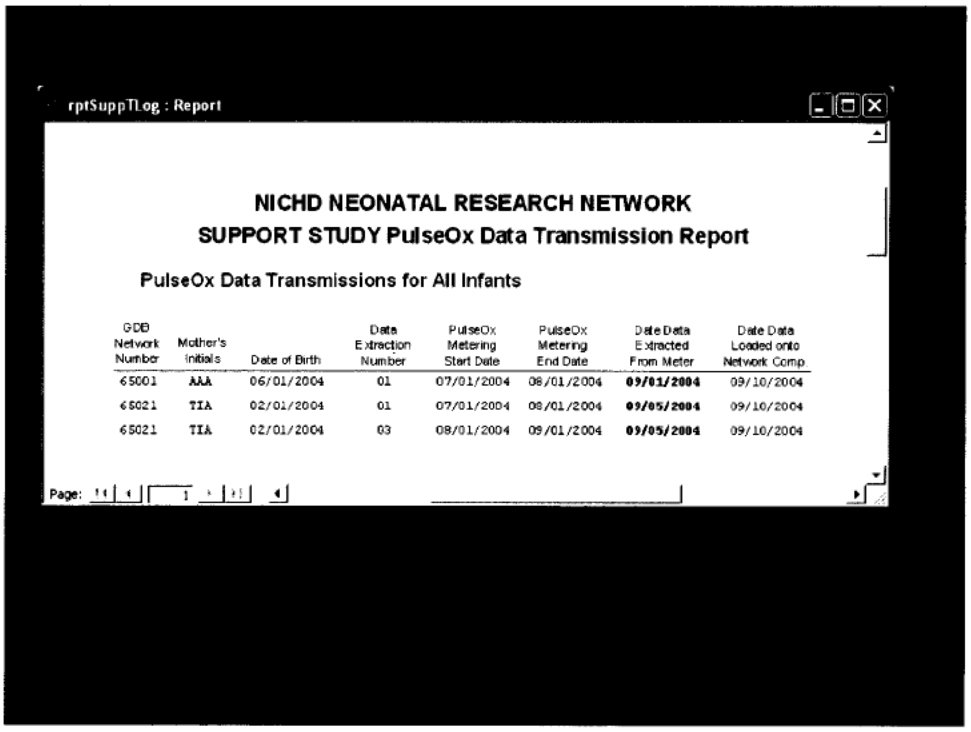
If you don't know, experiment. This is all that will happen if you are wrong.

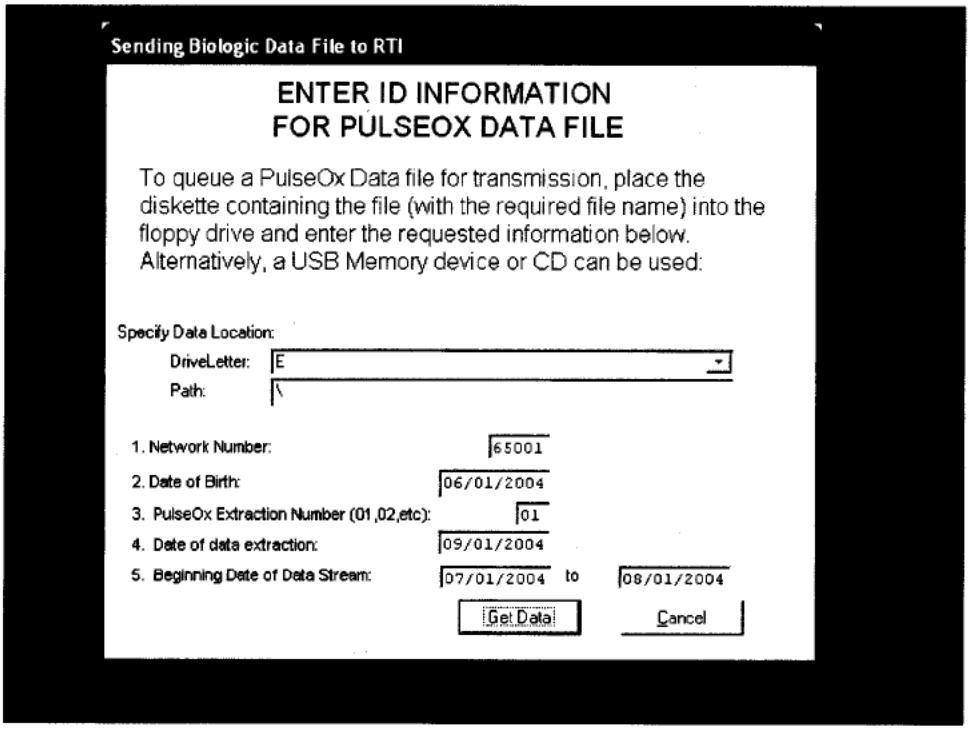


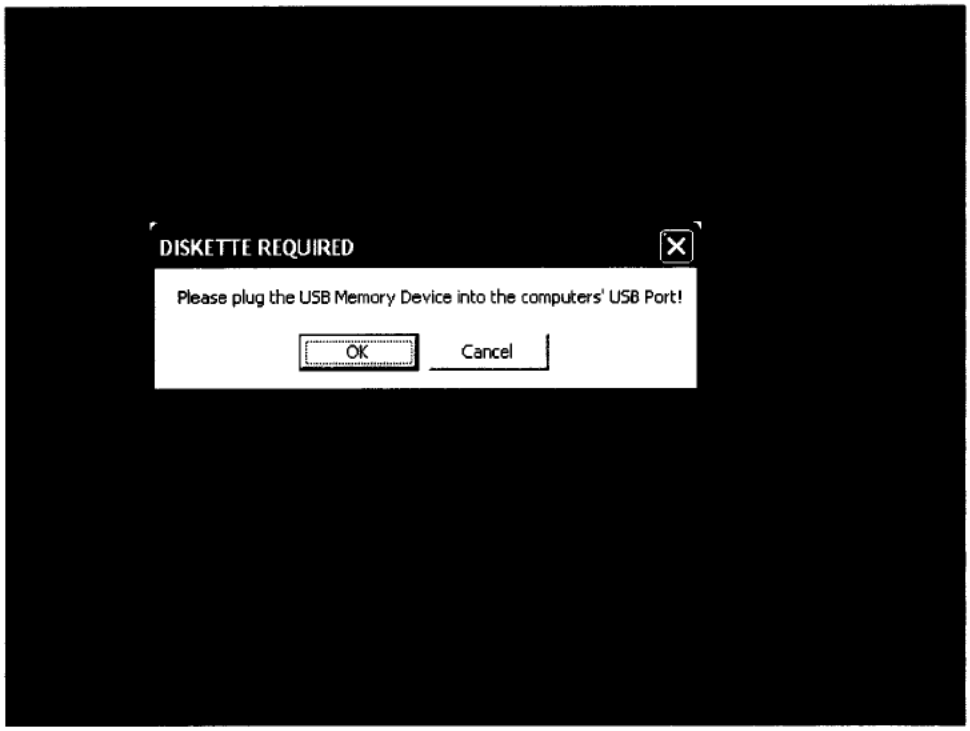
Hit Extraction.

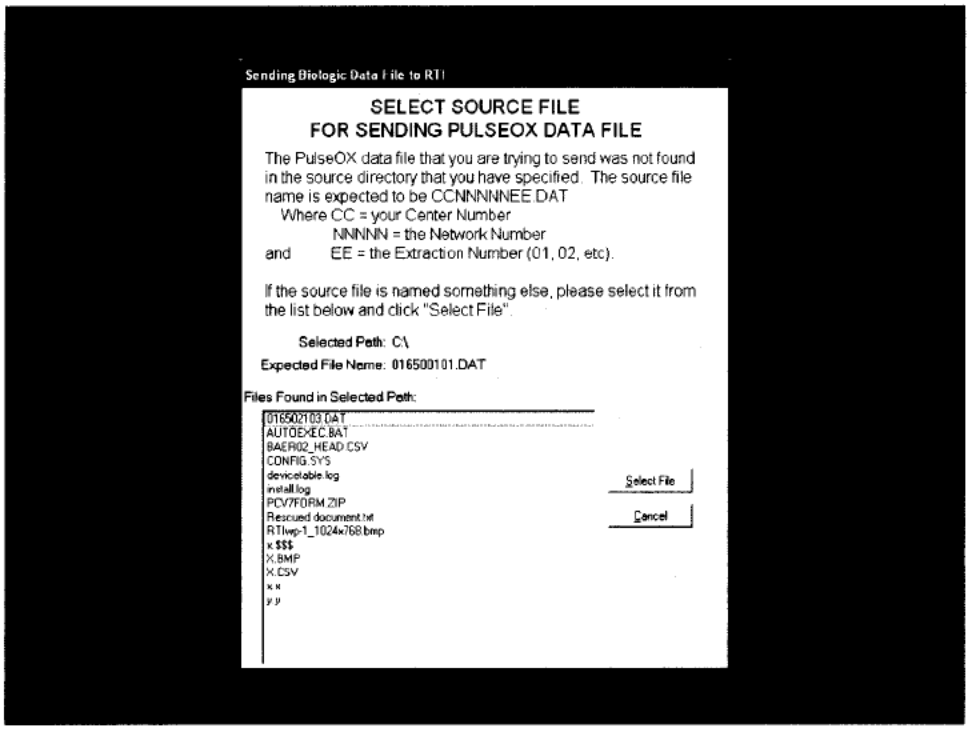


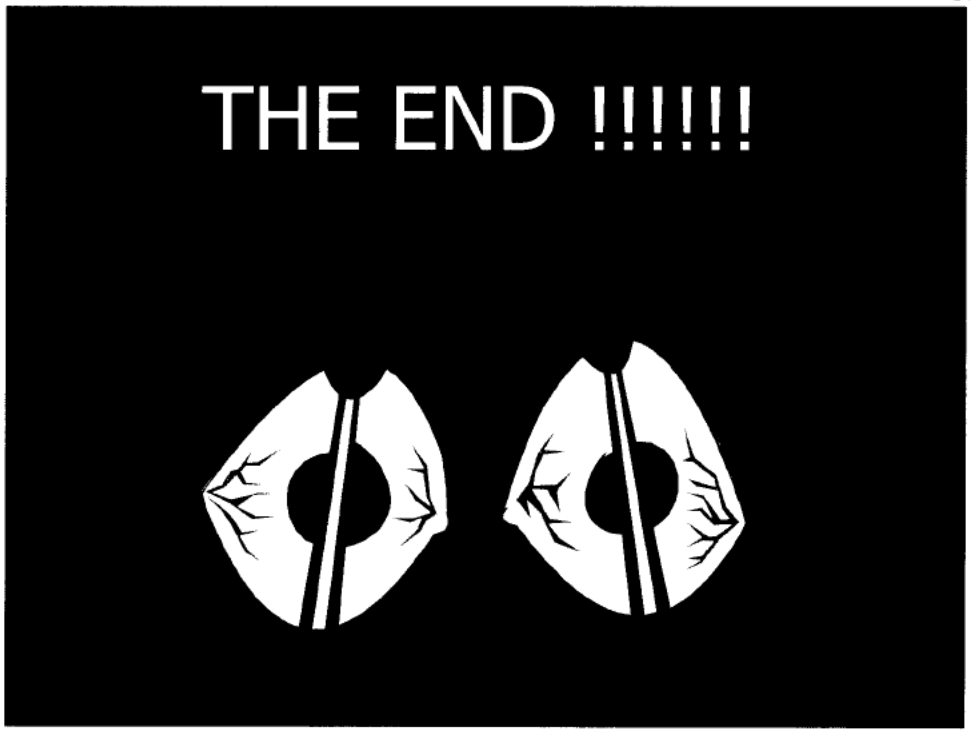












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

 # xxxx

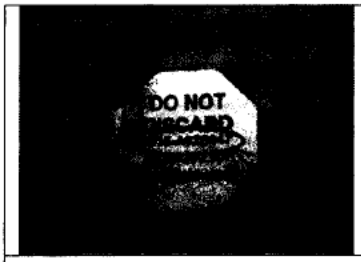
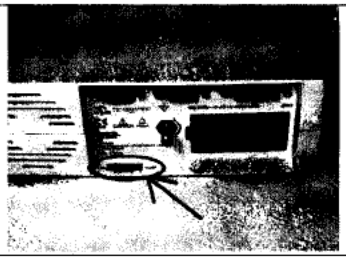
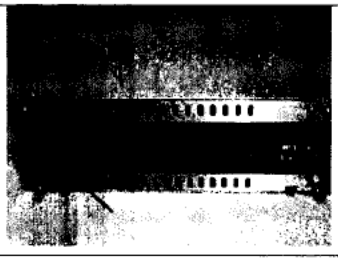
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

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 ≥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
   Complete this question only if Q.B.1 = YES

   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
SAFETY MONITORING FORM
DRAFT

SUPP05 version 4.0
October 3, 2005
Revised March 7, 2006
Revised November 1, 2006

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: ___

Complete a form each day through DOL 14 **1. Study Day:** ___ **2. Date:** ___ / ___ / _____.

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	___ : ___	__.___	___	__.___	___
2. 04 : 00	___ : ___	__.___	___	__.___	___
3. 06 : 00	___ : ___	__.___	___	__.___	___
4. 08 : 00	___ : ___	__.___	___	__.___	___
5. 10 : 00	___ : ___	__.___	___	__.___	___
6. 12 : 00	___ : ___	__.___	___	__.___	___
7. 14 : 00	___ : ___	__.___	___	__.___	___
8. 16 : 00	___ : ___	__.___	___	__.___	___
9. 18 : 00	___ : ___	__.___	___	__.___	___
10. 20 : 00	___ : ___	__.___	___	__.___	___
11. 22 : 00	___ : ___	__.___	___	__.___	___
12. 23 : 59	___ : ___	__.___	___	__.___	___

5. Oximeter Alarm Checks Q6hr/day

a. ___ : ___
b. ___ : ___
c. ___ : ___
d. ___ : ___

6. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: ___

4. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 08 : 00	___ : ___	__.___	___	___	__.___	___	___	__.___	___
2. 16 : 00	___ : ___	__.___	___	___	__.___	___	___	__.___	___
3. 23 : 59	___ : ___	__.___	___	___	__.___	___	___	__.___	___

* Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

DRAFT

SUPP05A version 4.0
Revised June 5, 2006
Revised November 1, 2006

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Report ~~This form should be completed~~ each time an intubation/extubation occurs after admission to the NICU through DOL 14. ~~in the same day.~~ Number each event sequentially.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
   If yes

   a. Record the time of intubation __ __ : __ __ (Hr : Min)

   b. Record the following prior to intubation :
   1. Were blood gases obtained within 6 hours prior to the event? Y N
      If yes,
      a. pH __. __ __
      b. PCO_2 __ __ __
   2. FiO_2 __. __ __
   3. Saturation __ __ __
   4. Apnea? Y N
   5. Sepsis/R/O Sepsis? Y N
   6. Hemodynamic instability? Y N
   7. Clinically significant PDA? Y N
   8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
   If Yes,

   a. Record the time of extubation __ __ : __ __ (Hr : Min)

   b. Type of extubation: __

1= Planned	2= Accidental

   c. Record the following prior to extubation
   1. Were blood gases obtained within 6 hours prior to the event? Y N
      If yes,
      a. pH __. __ __
      b. PCO_2 __ __ __
   2. FiO_2 __. __ __
   3. Saturation __ __ __

Initials of person completing this form: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
   If yes

   a. Record the time of intubation __ __ : __ __ (Hr : Min)

   b. Record the following prior to intubation :
   1. Were blood gases obtained within 6 hours prior to the event? Y N
      If yes,
      a. pH __. __ __
      b. PCO_2 __ __ __
   2. FiO_2 __. __ __
   3. Saturation __ __ __
   4. Apnea? Y N
   5. Sepsis/R/O Sepsis? Y N
   6. Hemodynamic instability? Y N
   7. Clinically significant PDA? Y N
   8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
   If Yes,

   a. Record the time of extubation __ __ : __ __ (Hr : Min)

   b. Type of extubation: __

1= Planned	2= Accidental

   c. Record the following prior to extubation
   1. Were blood gases obtained within 6 hours prior to the event? Y N
      If yes,
      a. pH __. __ __
      b. PCO_2 __ __ __
   2. FiO_2 __. __ __
   3. Saturation __ __ __

Initials of person completing this form: __ __ __

The Surfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Replacement Oximeter Form

DRAFT

Center: __ __ **Site:** ___ **Network No.** __ __ __ __ **Birth No.** ___ **Mother's Initials:** __ __ __

Complete this form each time a study oximeter is replaced from study initiation to 36 weeks or status.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
2.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
3.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
4.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
5.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
6.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
7.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
8.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
9.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
10.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___

PROTOCOL DEVIATION FORM

DRAFT

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)*~~
   11. Infant randomizes to incorrect gestational age group
   12. Postnatal steroids given for BPD/CLD within 21 days of life.
   99. 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: __ __ __

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: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

OUTCOME STATUS FORM

SUPP09 version 2.1
January 4, 2005
Revised October 26, 2005
Revised November 1, 2006

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 or withdrawn (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	6 = Withdrawn from study

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
2= Betamethasone
3= Hydrocortisone
4= Prednisone
5= Other (Specify)_____

Initials of person completing this form: __ __ __

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Randomized list of Support accrual at UAB
Date: Thursday, November 16, 2006 1:28:32 PM

---

fyi, Kris will not be there either.
wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, November 16, 2006 10:21 AM
To: Wade Rich
Cc: Petrie, Carolyn
Subject: RE: Randomized list of Support accrual at UAB

Me either – leaving shortly to go out of town – Support revisions (all of them) will be sent out before I leave.- Thanks!
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, November 16, 2006 1:22 PM
To: Zaterka-Baxter, Kristin
Cc: Petrie, Carolyn
Subject: RE: Randomized list of Support accrual at UAB

Carolyn, Kris,
I need a quick update on anything you would want me to present on the Coord Call for Neil, who will not be available.
Wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, November 16, 2006 8:19 AM
To: Wade Rich
Cc: Pickett, James; Das, Abhik
Subject: RE: Randomized list of Support accrual at UAB

I think all three of us will be reviewing all charts – James is the expert in interpreting the data reports from RTI, I can help with SAE IRB/consents and you have the expertise in the patient population, NICU and protocol. The first day will most like be all chart review. The second day James can meet with the DE people (for a couple of hours so he can see how they function, if he can answer any questions or give any advice in that process – we'll have missing forms report and batch edits etc..) and you and I can go to the NICU and IRB (depending on their availability). One thing I didn't think of was Support FU – we'll do chart reviews for that but as far as having the FU staff available and present at the summary visit, they should be included. James will probably want to talk with he DE FU people as well if they're not the same as NICU.

The agenda doesn't need to be hour by hour, just day by day to give them an idea of what we want to

review and to give them the flexibility to schedule things by hour (ie, when it's a good time to go to the NICU, when their IRB has available time etc.). Sorry I wasn't too clear on that – to clarify a bit more about who and when, I mean; Monica (and/or Shirley and Vivian) will need to be present when we arrive to let us know where we will be spending the day and a brief overview of how their charts are set up, then just available if we have any questions (we'll need to know how to contact them if we do). Then, on the second day, will need to schedule time take us to their IRB if they can't pull the IRB charts; they won't need to be present during the review; just be available for questions (if their IRB can only meet Thursday, that's fine too – we're accommodating). They will need to be present for the NICU tour and the DE people will need to be present with James (I'm guessing about 2 hours or so – it's up to him though – James?) Thanks for asking all this – appreciate it! I realize you are the monitor and we're assisting you so please feel free to adjust anything you see fit.
Thanks much,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, November 16, 2006 10:36 AM
To: Zaterka-Baxter, Kristin
Subject: RE: Randomized list of Support accrual at UAB

Kris,
Is it your intent that some of these things will occur in tandem? I am not certain how much time James and you will need for the Coordinating Center items, or if the intent
is that they be done in tandem. Also, will I be the only one reviewing the 6 charts, or will you be doing that also? I can easily see the first day being nothing but chart review.

Wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, November 16, 2006 7:13 AM
To: Wade Rich
Cc: Das, Abhik; Pickett, James; Auman, Jeanette O.
Subject: FW: Randomized list of Support accrual at UAB

Hi Wade, The 14th and 15th of Dec. are fine with James as well. A letter needs to be generated to Dr. Carlo and Monica, copying Rose, for the site visit. The letter needs to include:

- A brief letter stating the reason why we are coming to monitor the Support study and who from RTI is monitoring (Wade Rich, James Pickett, and Kris Zaterka-Baxter; aka DCC Support Monitor and staff)
- The date we're planning to visit (12/14 and 12/15) and time we plan to start and end.
- An agenda (we will need to see IRB folders so may need to schedule time to go to their IRB if these charts can not be taken out of the IRB) and time to meet with Dr. Carlo and all research staff to go over the visit summary (should take about 45mins or so the end of the second day). It should also include a visit to the NICU. We need to let them know who needs to be present/or just available and when.
- The list of charts to be review (below) plus, we will be pulling one (active – in house) patient if available. We'll let them know what chart that will be about a week prior to the visit. Please note these charts and all Support secondary studies these infants have been enrolled in. We can

generate a list for them with this info if needed. We'll only be reviewing one or two items form these secondary charts and I can add these questions to the monitoring form and send it to you in a bit.

The letter needs to come from you on behalf of the DCC; do you have time to do this and get this to UAB by tomorrow? Attached is RTI's letter head (memo format – I can look for actual letter head and send that along shortly) that can be used. Please let me know if you don't have time and we can call instead and let them know the essentials and send the letter later. Please also let me know if you have any questions or if I can help in any way.
Thanks!
Kris

Kris Zaterka-Baxter, RN, CCRP
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4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

#	Network	Randomization (Support)
1	---	(b) (6)
2	---	
3	---	
4	---	
5	---	
6	---	

From: Zaterka-Baxter, Kristin
To: Julie Rohr; Conra Lacy
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins; Das, Abhik
Subject: RE: Support oximeters
Date: Thursday, November 16, 2006 11:42:26 AM

Thanks Julie – appreciate the list! Dr. Higgins and UAB (Monica, Shirley and Dr. Carlo) are the ones who helped out – the DCC just helps facilitate a bit. Monica's # at UAB is (205) 934-5771; two day delivery is fine. The NRN website staff directory is located at the following address just in case you need anything further (https://neonatal.rti.org). Glad we were able to help and please call or contact me by email if you have any questions.

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Wednesday, November 15, 2006 1:12 PM
To: Zaterka-Baxter, Kristin; Conra Lacy
Cc: Rosemary (NIH/NICHD) [E] Higgins; Monica Collins; Das, Abhik
Subject: Re: Support oximeters

Kris, thanks for the help in allowing us to keep the oximeters and docking stations that have already been checked by our clinical engineering department.
I am trying to get the 3 oximeters shipped to UAB and need a phone number for Monica Collins for the label. Also, what is the shipping priority - is second day OK or do they need them next day?
Just so you have accurate information on serial numbers I am including the actual numbers of the equipment that we have here at UNM.
OXIMETERS at NEW MEXICO :
329709 ORANGE docking station 74732 actual 062544
329689 ORANGE docking station 74768 actual 063208
329713 ORANGE docking station 73615
329703 ORANGE docking station 79445
329706 ORANGE docking station 74743 actual 063195
329083 BLUE docking station 77619
328935 BLUE docking station 75185
329207 BLUE docking station 73643 actual 062347
328981 BLUE docking station 79567
329168 BLUE docking station 74766
Thanks for your help.
Julie

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital

2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

>>> "Zaterka-Baxter, Kristin" < kzaterka@rti.org > 11/14/2006 5:36 am >>>

Hi Connie and Julie,
Please send the 3 ORANGE oximeters listed below to UAB. These are the ones Ellen sent you from Emory 11/07/06 and are originally Miamis (a collaborating center of the Network). Please keep the BLUE and ORANGE oximeters you currently have (listed below). These oximeters have been purchased and belong to UAB and will need to be sent back at study end or possibly sooner.
Your site was originally scheduled to receive oximeters from Miami. However, at the time your site was approved to begin recruitment, it was discovered the histograms on some of Miamis instruments needed adjustment, which required them to be sent back to Masimo. We asked UAB (who was holding the oximeters from Miami), to send these in for repair and send you 10 of their extra oximeters to avoid any delay in study start up. Because of the nature of the study and recruitment patterns, UAB is one of the designated sites that carry extra oximeters to distribute to sites as needed; sometimes receiving sites are asked to transfer the oximeters around if they are no longer being used, otherwise to send them back to the original site. Please let me know if you have any further questions; we are very willing to help if we can and please know we are always open to suggestions.
ORANGE FROM EMORY (now at NM) TO GO TO UAB :
317227 docking station 059866
317560 docking station 062543
317384 docking station 063202
OXIMETERS to keep at NEW MEXICO :
329709 docking station 74732
329689 docking station 74768
329713 docking station 73615
329703 docking station 79445
329706 docking station 74743
329083 BLUE docking station 77619
328935 BLUE docking station 75185

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Das, Abhik
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Pickett, James
Subject: RE: Revised Support Manual and approved forms revisions
Date: Wednesday, November 15, 2006 9:41:42 AM

I am loath to make any new form changes at this stage unless absolutely necessary and endorsed by the subcommittee.

Thanks

Abhik

From: Zaterka-Baxter, Kristin
Sent: Tuesday, November 14, 2006 6:22 PM
To: Das, Abhik
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Auman, Jeanette O.; Pickett, James
Subject: FW: Revised Support Manual and approved forms revisions

Hi,
Please see Dr. Yoder's response below to the Support Study revisions. I asked for comments to be in by today and this is the only one I've received. What do you think about Dr. Yoder's suggestion? Should I go ahead and send out the revisions; the reason why I ask primarily is because we added a new code for status (6= withdrawn from study) the subcom had not seen before and needed approval.
Thanks,
Kris

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Friday, November 10, 2006 7:17 PM
To: kurt.schibler@cchmc.org; nxs5@cwru.edu; Roger Faix; higginsr@mail.nih.gov; wcarlo@peds.uab.edu; Das, Abhik; Zaterka-Baxter, Kristin; Gantz, Marie; Petrie, Carolyn; nfiner@ucsd.edu; wrich@ucsd.edu; Michele.Walsh@uhhs.com; alaptook@wihri.org
Cc: Pickett, James; Auman, Jeanette O.
Subject: Re: Revised Support Manual and approved forms revisions

No problems with new or revised forms/manual except:
- Do we need to include a "reason" column/code for why the oximeter needed to be replaced?

BAY

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 11/09/06 4:23 PM >>>
Hi all,

Please find attached a drafted technical memo addressing the Support MOP revisions based on the new and approved forms revisions with one exception:

On the SUPP09, Outcomes Form, we've added a status code of "6 = withdrawn from study". The request was brought forth by Dr. Yoder and discussed with Drs. Finer and Das. We would now like to ask you to review and comment on this addition along with the review of the manual changes outline in the technical memo (also attached is a highlighted and clean copy of the actual manual and a highlighted copy of all approved forms; with the exception of SUPP09). Please note we have renumbered the newly created SUPP12 form (oximeter replacements) to the SUPP05B form for a more logical progression of forms and content in the manual.

Please send comments/suggestions or concerns by November 14th so we may implement the new forms as soon as possible.

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP

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Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Yvonne Vaucher
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; Martha G. Fuller
Subject: RE: Bayley
Date: Tuesday, November 14, 2006 12:55:12 PM

Rose,

The Bayley III video is scheduled for the first week in December. We will not be able to schedule a Bayley II until early next year due to current staffing constraints and our completely booked clinic schedule. As we have submitted several Bayley II videos previously, and we have windows opening soon for Support patients, we put our priority on doing the Bayley III first. This is the best we can do right now.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Attending Neonatologist
Director, Infant Special Care Follow-Up Program
Division of Neonatal/Perinatal Medicine
Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 14, 2006 6:43 AM
To: Neil Finer; Yvonne Vaucher; Martha G. Fuller
Subject: Bayley

Hi,
Martha has a child scheduled for the Bayley III video exam the first week of December and will obtain a child for Bayley II video shortly thereafter. Let me know if this is NOT correct.
Thanks for all the effort with 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: Zaterka-Baxter, Kristin
To: Monica Collins
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Support oximeters
Date: Tuesday, November 14, 2006 7:53:15 AM

Monica,
With the blue oximeters (below) sent back from Emory, do you have enough that are currently not being used at your site to send the Miami blues needing repair to Masimo?

BLUE FROM EMORY TO GO TO UAB:
312119 docking station 062524
312272 docking station 061833
312225 docking station 061797

Please keep all Miami oximeters for now and thanks, I know doing us a favor set you short two oximeters (from Miami, you should still have 8 [4 blue, 4 orange]). We're keeping close track of all oximeters and you will receive the oximeters you purchased at study end if not sooner.
Much appreciated,
Kris

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Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Tuesday, November 14, 2006 7:36 AM
To: 'Conra Backstrom'; 'JRohr@salud.unm.edu'
Cc: Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Monica Collins'
Subject: Support oximeters

Hi Connie and Julie,

Please send the 3 ORANGE oximeters listed below to UAB. These are the ones Ellen sent you from Emory 11/07/06 and are originally Miami's (a collaborating center of the Network). Please keep the BLUE and ORANGE oximeters you currently have (listed below). These oximeters have been purchased and belong to UAB and will need to be sent back at study end or possibly sooner.

Your site was originally scheduled to receive oximeters from Miami. However, at the time your site was approved to begin recruitment, it was discovered the histograms on some of Miami's instruments needed adjustment, which required them to be sent back to Masimo. We asked UAB (who was holding the oximeters from Miami), to send these in for repair and send you 10 of their 'extra' oximeters to avoid any delay in study start up. Because of the nature of the study and recruitment patterns, UAB is one of the designated sites that carry extra oximeters to distribute to sites as needed; sometimes receiving sites are asked to transfer the oximeters around if they are no longer being used, otherwise to send them back to the original site. Please let me know if you have any further questions; we are very willing to help if we can and please know we are always open to suggestions.

ORANGE FROM EMORY (now at NM) TO GO TO UAB:
317227 docking station 059866
317560 docking station 062543

317384 docking station 063202

OXIMETERS to keep at NEW MEXICO:
329709 docking station 74732
329689 docking station 74768
329713 docking station 73615
329703 docking station 79445
329706 docking station 74743
329083 BLUE docking station 77619
328935 BLUE docking station 75185

Thanks,
Kris

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Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Kristi Watterberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Conra Lacy; Julie Rohr
Subject: RE: SUPPORT Trial
Date: Monday, November 13, 2006 3:16:51 PM

Rose, I did ask you about the sensors, and received a reply from Wade Rich with two sensors listed to choose from, neither of which is apparently currently in use for the study.

I don't see that the request to change out our oximeters would have been different if we had had a training session at our site. We certainly do want a training session, and I've talked with Michelle about it, but we want to get things up and going before having her come out, so we would have a basis for our questions about various issues.

I can understand that it is difficult to bring new centers on in the middle of the study, as things have changed over time. Julie Rohr is very knowledgeable and experienced, especially with introduction of new equipment and protocols into the unit (she was the clinical nurse educator in the unit for many years). Connie and I are very glad to have her working with us on this study.

At least we're all approved and screening! Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 11/13/2006 11:56:51 am >>>

Hi,

I have requested that UAB allow the oximeters to remain at your site. Maribeth Sayre is the contact at Massimo. Many of the details such as probes, etc. can be solved with letting us know there is an issue. Much of this was covered at the training and on site training by the members of the subcommittee as sites get up and running. Let me know if there are other issues.

Thanks
Rose

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Friday, November 10, 2006 5:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; MSayre@masimo.com; vbishop@masimo.com; kzaterka@rti.org; Conra Lacy; Julie Rohr; Kristi Watterberg
Subject: SUPPORT Trial

Hello to everyone!

I am helping Dr. Watterberg and Connie Backstrom Lacy with the implementation of the Support Trial here at UNM. In trying to handle all the practical logistics of making this study happen I have encountered several instances where lapses in communication have resulted in duplicate work and frustration at our facility. My hope is that we can improve communication and eliminate unnecessary work. As the information that we needed was not in the study documents or MOP, a mechanism needs to be in place to make sure that centers initiating this study have the information that they need.

The most concerning example has to do with the 10 oximeters that we received for the study. They were inspected by our hospital Clinical Engineering Department per hospital and JCAHO standards. Now we are being asked to send these 10 oximeters out to different institutions around the country and bring in new oximeters. We have not been given a reason for this. This will necessitate Clinical Engineering repeating

all of their work with new oximeters, something that the director of their department is not able to do at this time because of their workload and is not willing to do without a valid reason. If the oximeters that we currently have function appropriately, then why can't we keep the ones that we currently have? If this is a bookkeeping problem with serial numbers then can't the problem be solved with correcting the paperwork instead of physically sending oximeters around the country in an elaborate switching sequence? Can the solution to whatever problem it is that exists be solved without asking our clinical engineering people to continue to repeat the same work?

Other examples include:
When inspecting the materials for the study it was clear that we did not have the sensors for the study or any information about obtaining them. Dr. Watterberg contacted Rosemary Higgins and received information from her and Wade Rich that we needed to order them from Masimo. As the Masimo rep for our area is not allowed in our hospital (or to call anyone here) I contacted the Masimo customer support number to order what we needed. Using the best information that I could get, we ordered what we felt would be the best choice for our babies in the study. It turns out that what we needed was not even an option that was presented.

I knew that we needed staff education on the use of the oximeters so when I was speaking to customer support I asked about getting a clinical specialist in for training. I was given Julie Bradley's name and number. I also e-mailed Mary Beth Sayre (the only name I could find in the materials) trying to ensure that we were able to meet our training requirements. It was greatly appreciated that Julie altered her schedule to come and do inservicing with our staff. This was her first exposure to the masked oximeters and the SUPPORT Trial and I appreciated her efforts to get information to answer our questions as they came up. As a result of the questions we found out that the sensors we had ordered were not the ones that we needed. She gave me Vickie Bishop's name and number as the person who could tell us what sensors needed to be used on the study.

When I contacted Vickie yesterday she seemed quite surprised to hear from me. She said that she had no idea that we were in the SUPPORT Trial and that she was the person who was supposed to send out the masked oximeters and keep track of the serial numbers. She was surprised to hear that we had received oximeters. (She was very helpful in arranging to get the sensors that we needed and the return of the wrong sensors.)

These are just some examples where having the appropriate information available would have saved a great deal of time and effort. My concerns at this point are to find a reasonable alternative to swapping out the oximeters and making sure that communication problems are corrected. In that regard, is there a primary contact person that I can go to for these kinds of questions or are there additional written materials that have the information we might need?

Thanks for your time.

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

From: Wade Rich
To: jrohr@salud.unm.edu; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; kwatterberg@salud.unm.edu; msayre@masimo.com
Subject: FW: SUPPORT Trial
Date: Monday, November 13, 2006 9:47:01 AM

Julie,

I do not know why your oximeters were shipped elsewhere. Rose will know. The system was set up such that centers would not have to give up their core oximeters. A small group of centers was established which would have a stock of oximeters available to ship to any center that needed them. Because a site needs enough devices of both colors to cover pending deliveries, a couple of sets of multiples can leave you short in a big hurry. I believe each of the centers have 10 spares, but that may have changed in this go around. As to sensors, I apologize for the inconvenience. When we wrote this study three years ago, and then got it rolling, the sensors were part of the initial shipments, and we discussed them in great detail. Because of contract issues, centers had to come up with a way that worked for them to integrate the sensors into their system. I did not, I fully admit, even consider the need to bring new centers up to speed on the study from a position outside the network. That being said, nothing I could have written would have worked at your center anyway if you are not allowed to have Masimo people at your site. Vicki Bishop has shipped every oximeter that has been a part of the trial, so I find that statement a little difficult to comprehend. Maybe she did not understand what you meant.

I think Rose needs to help you with the other issues. Let me know if there is anything else I can assist you with.

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(b) (6)

From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Saturday, November 11, 2006 5:09 AM
To: Wade Rich
Subject: FW: SUPPORT Trial

Fyi

Maribeth

-----Original Message-----
From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Fri Nov 10 14:41:24 2006
To: higginsr@mail.nih.gov; Maribeth Sayre; Vicki Bishop; kzaterka@rti.org; Conra Lacy; Julie Rohr; Kristi Watterberg
Subject: SUPPORT Trial

Hello to everyone!

I am helping Dr. Watterberg and Connie Backstrom Lacy with the implementation of the Support Trial here at UNM. In trying to handle all the practical logistics of making this study happen I have encountered several instances where lapses in communication have resulted in duplicate work and frustration at our facility. My hope is that we can improve communication and eliminate unnecessary work. As the information that we needed was not in the study documents or MOP, a mechanism needs to be in place to make sure that centers initiating this study have the information that they need.

The most concerning example has to do with the 10 oximeters that we received for the study. They were inspected by our hospital Clinical Engineering Department per hospital and JCAHO standards. Now we are being asked to send these 10 oximeters out to different institutions around the country and bring in new oximeters. We have not been given a reason for this. This will necessitate Clinical Engineering repeating all of their work with new oximeters, something that the director of their department is not able to do at this time because of their workload and is not willing to do without a valid reason. If the oximeters that we currently have function appropriately, then why can't we keep the ones that we currently have? If this is a bookkeeping problem with serial numbers then can't the problem be solved with correcting the paperwork instead of physically sending oximeters around the country in an elaborate switching sequence? Can the solution to whatever problem it is that exists be solved without asking our clinical engineering people to continue to repeat the same work?

Other examples include:
When inspecting the materials for the study it was clear that we did not have the sensors for the study or any information about obtaining them. Dr. Watterberg contacted Rosemary Higgins and received information from her and Wade Rich that we needed to order them from Masimo. As the Masimo rep for our area is not allowed in our hospital (or to call anyone here) I contacted the Masimo customer support number to order what we needed. Using the best information that I could get, we ordered what we felt would be the best choice for our babies in the study. It turns out that what we needed was not even an option that was presented.

I knew that we needed staff education on the use of the oximeters so when I was speaking to customer support I asked about getting a clinical specialist in for training. I was given Julie Bradley's name and number. I also e-mailed Mary Beth Sayre (the only name I could find in the materials) trying to ensure that we were able to meet our training requirements. It was greatly appreciated that Julie altered her schedule to come and do inservicing with our staff. This was her first exposure to the masked oximeters and the SUPPORT Trial and I appreciated her efforts to get information to answer our questions as they came up. As a result of the questions we found out that the sensors we had ordered were not the ones that we needed. She gave me Vickie Bishop's name and number as the person who could tell us what sensors needed to be used on the study.

When I contacted Vickie yesterday she seemed quite surprised to hear from me. She said that she had no idea that we were in the SUPPORT Trial and that she was the person who was supposed to send out the masked oximeters and keep track of the serial numbers. She was surprised to hear that we had received oximeters. (She was very helpful in arranging to get the sensors that we needed and the return of the wrong sensors.)

These are just some examples where having the appropriate information available would have saved a great deal of time and effort. My concerns at this point are to find a reasonable alternative to swapping out the oximeters and making sure that communication problems are corrected. In that regard, is there a primary contact person that I can go to for these kinds of questions or are there additional written materials that have the information we might need?

Thanks for your time.

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

From: Zaterka-Baxter, Kristin
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT Trial
Date: Monday, November 13, 2006 7:58:32 AM
Attachments: Masimo oximeter probes.msg
SUUPORT OXIMETERS.msg
RE Support oximeters.msg
FW Masimo.msg

My apologies, I shouldn't' have sent the earlier email without further clarification. I've attached four emails; one giving instruction on how to order oximeter probes/sensors, a second contact email from Marybeth Sayre (forwarded from me to NM) explaining about Masimo in services but with clarification that the intent for the new centers was to have a PI come for a study start up/site visit and they would be able to help with the oximeters, a third email to the new centers explaining that they will receive oximeters for the outgoing centers, and finally, an email from UAB asking for the NM oximeters back.

There was a problem at the time NM was to receive oximeters from Miami; NM received IRB approval and sent a request for oximeters at the same time we discovered the Miami oximeter histograms had a problem when used at UAB. UAB also had ten extra (still in the box) oximeters for which they just received the treatment codes. The Miami oximeters were suppose to go to NM but now the blues needed to go back to Masimo for repair, I asked UAB to send NM the 10 still in the box and asked them to keep the ones from Maimi once repaired. I thought this was clear and agreed but after querying UAB to see if they had received the Miami oximeters back from Masimo, I received an email from UAB stating they were not able to send them for repair because that would have left them short and that once they received the oximeters back from NM (email also attached), they would send the Miami blues for repair. I called Monica to clarify and stated I thought we had originally agreed on something different however, Monica said they paid to have the 10 extra on site to send to other sites as needed and would like to have the ones sent to NM returned. Hence the oximeter shuffle. Please let me know if you need further info or if I can do anything to help correct the situation at NM.

Thanks,

Kris

From: Zaterka-Baxter, Kristin
Sent: Saturday, November 11, 2006 10:04 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Das, Abhik
Subject: FW: SUPPORT Trial

Hi,

Please see attached. Sounds like Masimo may have internal communication problems. As for everything else listed below, I guess we could have made it more clear that the DCC should be the first contact; we have the answer to all those questions and could have prevented the run around.

Thanks,

Kris

From: Julie Rohr [mailto:JRohr@salud.unm.edu]
Sent: Friday, November 10, 2006 5:37 PM
To: higginsr@mail.nih.gov; MSayre@masimo.com; vbishop@masimo.com; Zaterka-Baxter, Kristin; Conra

Lacy; Julie Rohr; Kristi Watterberg
Subject: SUPPORT Trial

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Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: FW: SUPPORT Trial
Date: Saturday, November 11, 2006 10:03:34 AM
Attachments: RE SUPPORT.msg

Hi,

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Thanks,

Kris

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Sent: Friday, November 10, 2006 5:37 PM
To: higginsr@mail.nih.gov; MSayre@masimo.com; vbishop@masimo.com; Zaterka-Baxter, Kristin; Conra Lacy; Julie Rohr; Kristi Watterberg
Subject: SUPPORT Trial

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number. I also e-mailed Mary Beth Sayre (the only name I could find in the materials) trying to ensure that we were able to meet our training requirements. It was greatly appreciated that Julie altered her schedule to come and do inservicing with our staff. This was her first exposure to the masked oximeters and the SUPPORT Trial and I appreciated her efforts to get information to answer our questions as they came up. As a result of the questions we found out that the sensors we had ordered were not the ones that we needed. She gave me Vickie Bishop's name and number as the person who could tell us what sensors needed to be used on the study.

When I contacted Vickie yesterday she seemed quite surprised to hear from me. She said that she had no idea that we were in the SUPPORT Trial and that she was the person who was supposed to send out the masked oximeters and keep track of the serial numbers. She was surprised to hear that we had received oximeters. (She was very helpful in arranging to get the sensors that we needed and the return of the wrong sensors.)

These are just some examples where having the appropriate information available would have saved a great deal of time and effort. My concerns at this point are to find a reasonable alternative to swapping out the oximeters and making sure that communication problems are corrected. In that regard, is there a primary contact person that I can go to for these kinds of questions or are there additional written materials that have the information we might need?

Thanks for your time.

Julie Rohr MSN RNC
Nurse/Clinical Trials Coordinator
Department of Pediatrics
UNM Hospital
2211 Lomas Blvd NE
Albuquerque, NM 87106
(505) 272-0363

Blansfield, Earl (NIH/NICHD) [E]

From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tuesday, June 13, 2006 3:51 PM
To: MSayre@masimo.com
Cc: Petrie, Carolyn; wrich@ucsd.edu
Subject: RE: SUPPORT
Attachments: NRN site (PIs Coords) Contact list[05.16.06].doc

Hi Marybeth,
Please find attached a list of NRN coordinator/PI contacts; exiting centers and entering centers in 2006. Please make a note to send all masimo oximeter information (shipments with serial numbers and high/low assignments) to me prior to sending the actual shipments to any of the sites. I'll be keeping track for the data coordinating center. Please let me know if you have any questions.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Petrie, Carolyn
Sent: Sunday, June 11, 2006 10:52 PM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT

Kris-

Do you have a contact list that you could send her? I wasn't sure if I should send her the website information (just on the homepage). I am out of the office Mon and Tues attending a conference with Rose so will have limited access to email.

So nice to see you last week!
Carolyn

From: Wade [mailto:wrich@ucsd.edu]
Sent: Friday, June 09, 2006 6:33 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT

Carolyn,
Can you send this info to Maribeth at Masimo?
wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Friday, June 09, 2006 3:14 PM
To: Wade Rich (E-mail)
Subject: SUPPORT

Hi Wade,

Could you please send me a list of the centers that were dropped, and a list of the centers that were added? If you have info about contact people at the new centers, that would also be useful.

Thanks,
Maribeth

May 16, 2006

NICHD NEONATAL NETWORK
Contacts

Exiting Centers in 2006

Center 08: University of Miami
PI: Shahnaz Duara, M.D.
University of Miami
Jackson Memorial Hospital
1400 NW 10th Avenue
P.O. Box 016960 (R-131)
Miami, Fl 33136
Phone: (305) 243-6408
FAX: (305)243-6581
E-mail: sduara@miami.edu

Coordinator: Ruth Everett, R.N.
University of Miami
Dominion Towers, 8th Floor (M827)
1400 NW 10th Avenue
P.O. Box 016960
Miami, Fl 33136
Phone: (305) 243-6884
FAX: (305)243-6581
E-mail: Reverett@med.miami.edu

Center 20: Wake Forest University
PI: Michael O'Shea, M.D., M.P.H.
Dept. of Pediatrics
WFU School of Medicine
Medical School Blvd.
Winston-Salem, NC 27517
Phone: (336) 716-2529
FAX: (336) 716-2525
E-Mail: moshea@wfubmc.edu

Coordinator: Nancy Peters, R.N.
Dept. of Pediatrics
WFU School of Medicine
Medical School Blvd.
Winston-Salem, NC 27517
Phone: (336) 716-6911
FAX: (336) 716-2525
E-Mail: npeters@wfubmc.edu

Center 21: University of Rochesters
PI: Dale L. Phelps, M.D.
Division of Neonataology

Children's Hospital at Strong
601 Elmwood Ave., Box 651
Rochester, NY 14642
Phone: (716) 275-2972
FAX: (716) 461-3614
E-Mail: dale_phelps@urmc.rochester.edu

Cpprdinator: Linda Rubens, R.N.
Division of Neonataology
Children's Hospital at Strong
601 Elmwood Ave., Box 651
Rochester, NY 14642
Phone: (716) 275-0218
FAX: (716) 461-3614
E-Mail: linda_rubens@urmc.rochester.edu

Center 22: University of California--San Diego

PI: Neil Finer, M.D.
University of California--San Diego
200 W. Arbor Drive, 8774
San Diego, CA 9103-8774
Phone: (619) 543-3759
E-Mail: nfiner@ucsd.edu

Coordinator: Wade Rich, RRT-NPS
Division of Neonatology
University of California--San Diego
200 W. Arbor Drive, 8774
San Diego, CA 9103-8774
Phone: (619) 543-5375
E-Mail: wrich@ucsd.edu

Entering (New) centers in 2006

Center 23: Tufts NEMC

PI: Ivan D. Frantz III, MD
Department of Pediatrics
Floating Hospital
Tufts-New England Medical Center
750 Washington St.
Boston, MA 02111
617-636-5322
617-636-8391 (FAX)
ifrantz@tufts-nemc.org

Coordinator: Anne Furey, M.P.H.
NRN Research Coordinator
Division of Newborn Medicine
The Floating Hospital for Children
750 Washington Street, Tufts-NEMC #44

Boston, MA 02111
Phone: 617-636-1218
Fax: 617-636-1456
Pager: 617-604-(b)
Email: afurey@tufts-nemc.org

Center 24: University of Iowa
PI: Edward F. Bell, MD
Professor of Pediatrics
University of Iowa
200 Hawkins Drive, 8811 JPP
Iowa City, IA 52242
319-356-4006
319-356-4685 (FAX)
Edward-bell@uiowa.edu

Coordinator: Karen J. Johnson, R.N.
Department of Pediatrics
University of Iowa
200 Hawkins Drive, 8900 JPP
Iowa City, IA 52242
319-356-2924
karen-johnson@uiowa.edu

Center 25: University of Utah
PI: Roger G. Faix, MD (PI)
Ross Milley, MD (Division chief – Neonatology)
Dept of Pediatrics
Williams Building
PO Box 581289
Salt Lake City UT 84158
801-581-7052
801-585-7085 (FAX)
Roger.faix@hsc.utah.edu
ross.milley@hsc.utah.edu

Coordinator: Susan Tepper, RN
Division of Neonatology, Department of Pediatrics University of Utah School of Medicine
295 Chipeta Way
Salt Lake City, UT 84108

Address for US Mail:
Susan Tepper, RN
Division of Neonatology, Department of Pediatrics University of Utah School of Medicine
P.O. Box 581289 Salt Lake City, UT 84158
Phone 801-581-7052
Fax 801-585-7395
e-mail susan.tepper@hsc.utah.edu

Center 26 : University of New Mexico
PI: Kristi Watterberg, MD (PI)
Alt. PI: LuAnn Papile, MD (Alt PI)

Dept of Pediatrics/Neonatology
MSC10 5590
University of New Mexico
Albuquerque, NM 87131
505-272-0180
505-272-1539 (FAX)
kwatterberg@salud.unm.edu
papile@unm.edu

Coordinator: Conra (Connie) Backstrom Lacy
Mailing and "overnight delivery" address:
Pediatric Clinical Research
MSC10 5590
University of New Mexico
Albuquerque, NM 87131-0001
Phone - (505) 272-0367,Digital Pager - (505) 951-(b) , Fax - (505) 272-6845
e-mail: cbackstrom@salud.unm.edu

Existing Centers with new coordinators and/or new PI contacts for 2006.

Center 04: University of Texas
New PI: Pablo Sanchez, MD
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd
Dallas, Texas 75390-9063
Phone:
Pablo.Sanchez@UTSouthwestern.edu

New Coordinator: Nancy Miller, R.N.
Department of Pediatrics
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., E3 404
Dallas, Texas 75235-9063
Phone: (214) 648-3780
FAX: (214) 648-2481
E-mail: Nancy.Miller@UTSouthwestern.edu

Center 11: University of Cincinnati
New PI: Kurt Schibler, MD
Cincinnati Children's Hospital Medical Ctr
3333 Burnet Ave
Cincinnati, OH 45229
Phone: (513) 636-4830
Fax: (513) 636-7868 Schibler, Kurt R MD
kurt.schibler@cchmc.org

Center 12: Indiana University
New PI: Brenda Poindexter, MD
Section of Neonatal-Perinatal Medicine
Indiana University School of Medicine

699 West Drive, RR 208
Indianapolis, IN 46202-5119
Phone: 317-274-4920
Fax: 317-274-2065
Email: bpoindex@iupui.edu

Center 14: Brown University
New PI: Abbot Laptook, MD
Department of Pediatrics
Women & Infants Hospital of Rhode Island
101 Dudley Street, Suite 1100
Providence, RI 02905
Phone: (401) 274-1122 x 1221
Fax: (401) 453-7571
Email: alaptook@wihri.org

From:	Zaterka-Baxter, Kristin
To:	nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; Walsh, Michele; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; wrich@ucsd.edu; Petrie, Carolyn
Cc:	Auman, Jeanette O.; Pickett, James
Subject:	Revised Support Manual and approved forms revisions
Date:	Thursday, November 09, 2006 6:23:24 PM
Attachments:	SUP10.doc SUPPORT Manual[uc]20061101.doc SUPPORT Manual[cc]20061101.doc SUPP04NICUAdmission[uc]20061101.doc SUPP05SafetyMonitor[uc]20061101.doc SUPP05ASafetyMonitor[uc]20061101.doc SUPP05BOximeterReplacement[uc]20061101.doc SUPP06 Prot Dev][uc]20061101.doc SUPP08Adverse Event[uc]20061101.doc SUPP09OutcomeForm[uc]20061106.doc

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Hi all,
Please find attached a *drafted* technical memo addressing the Support MOP revisions based on the new and approved forms revisions with one exception:

On the SUPP09, Outcomes Form, we've added a status code of *"6 = withdrawn from study"*. The request was brought forth by Dr. Yoder and discussed with Drs. Finer and Das. We would now like to ask you to review and comment on this addition along with the review of the manual changes outline in the technical memo (also attached is a highlighted and clean copy of the actual manual and a highlighted copy of all approved forms; with the exception of SUPP09). Please note we have renumbered the newly created SUPP12 form (oximeter replacements) to the SUPP05B form for a more logical progression of forms and content in the manual.

Please send comments/suggestions or concerns by November 14th so we may implement the new forms as soon as possible.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

RTI INTERNATIONAL | **Memorandum**

November 9, 2006

SUPPORT TECHNICAL MEMO # 10

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Manual of Procedures and Forms revisions (SUPP04, 05, 05A, 05B (new), 06. 08 and 09). Version Date November 1, 2006.

Please find below an outline of revisions made to the Manual (version date 11/01/06). All corresponding revised forms are enclosed. Please note all added text appears red and underlined and all ~~deleted~~ text appears red and stricken through.

Chapter 1, Overview and Trial Design, Forms descriptions (page 1-3 and 1- 4)

Safety Monitoring Form (SUPP05A)
This form is to be completed each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Safety Monitoring Form (SUPP05A)
This form is to be completed each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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~~.

Outcome Status Form (SUPP09)
This form will be completed when the infant is discharged home, transferred, if hospitalized at 120 days, ~~or~~ death or withdrawn (whichever comes first).

Chapter 9, Admission to NICU, SUPP04 (page 9-2)

Q.B.2
2. Was a blood gas done within 30 minutes prior to intubation?
Note: Complete this question only if question B.1 = YES

Chapter 10, Safety Monitoring, Form SUPP05, 05A and 05B

SUPP05 (page 10-1)

Q.3

3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.

~~10.2.1 Section A. Blood gas results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59. If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.~~

~~*Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.*~~

Q.3.b

b. Time Measured

~~For blood gas information~~ rRecord the actual time that the FiO2 was obtained ~~blood samples were collected~~ based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

Q.3.f (page 10-2)

f. FiO_2

Record the FiO_2 at the ~~time the blood gas was collected or at other~~ scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

Q.3.h

h. Mode of Support

Record the respiratory support as:

9= No Support all day and off Study oximeter

Q.4

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

Q.4.a

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

Q.4.b

b. Time Measured

~~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.~~

~~For all other time points enter the FiO_2 and Mode of Support.~~

Q.4.f (page 10-3)

f. FiO_2

Record the FiO_2 corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

Q.4.h

h. Mode of Support

9= No Support all day and off Study oximeter

Old Supp05 Q.14 (a new form has been created to capture replacement oximeters SUPP05B)

~~**14 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**~~

Old Supp05 Q.15 changes to Q.6

~~15~~ 6. Was the infant intubated or extubated on this day?

If Yes, Complete ~~Section B and/or Section C of~~ the SUPP05A

SUPP05A, (page 10-4)

DCC Note: since section B and/or C have been removed from the form, the primary change in this section is the renumbering of the form questions. One question has been added regarding blood gases prior to intubation/extubation in two sections of the form and in the manual

Old Section 10.2.2, Section B

10.3 ~~**2.2 Section B**~~. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question ~~15~~ 6 on the SUPP05 is coded "Yes". If more than one intubation/extubation occurs complete a new report ~~Section B~~ for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number

Consecutively number each event as reported on ~~Section B of~~ the SUPP05a form.

Q.3.b.1(intubation) and the same question for Q.4.c.1 (extubation)

1. Were blood gases obtained within 6 hours prior to the event?

~~*Record*~~ *Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.* ~~*, record "*"*~~

SUPP05B (page 10-5)

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. **Episode Number**
Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. **Date Oximeter Replaced**
Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. **Time Oximeter Replaced**
Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. **Replacement Oximeter Serial Number**
Record the six digit serial number of the replacement oximeter used.

e. **Replacement Oximeter Color Code**
Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

Chapter 11, Protocol Deviation, Form SUPP06, page 11-1

Q.2 (option 11, 12 and other code)
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
~~10~~99= Other: Specify type of protocol deviation

Chapter 13, Serious Adverse Experience, Form SUPP08 (page 13-1)

Q.1
~~**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.**~~ Record a consecutive Report Number in the header for each form submitted. This form should be completed and keyed at the sites as soon as possible.

1. Air leak ~~in the first 14 days~~

Chapter 14, Outcome Status, From SUPP09 (page 14-1)

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 or withdrawn (which ever comes first).

DCC Note: this status code has been added:

- **Withdrawn form study**
  Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

Cc Rosemary Higgins, MD

Enclosed: Forms SUPP04, SUPP05, SUPP05A, SUPP05B, SUPP06, SUPP08, SUPP09, Manual of Procedures (highlighted revisions and clean copy)

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006
Revised November 1, 2006

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 each time an ~~if more than one~~ intubation/extubation occurs ~~in the same day~~ after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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 or withdrawn (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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, 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 Duará, 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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. Any subsequent extubations will also follow standard practice.

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. $pC0_2$:

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 $Sa0_2$ ≥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?
Note: Complete this question only if question B.1 = YES

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
SUPP05 SUPP05A SUPP05B

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

1. Study Day: Enter the day this form is being completed.
2. Date: Enter the date that corresponds to the Study Day.
3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.
~~10.2.1 Section A. Blood gas results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**~~

~~*Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.*~~

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

~~For blood gas information~~ ~~r~~Record the actual time that the FiO2 was obtained ~~blood samples were collected~~ based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

f. FiO_2
Record the FiO_2 at the ~~time the blood gas was collected or at other~~ scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

4j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. ~~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.~~
~~For all other time points enter the FiO_2 and Mode of Support.~~

c. pH
Record the acid base status of the blood.

d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

g. Source:
Record the source of the blood gas
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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

~~13~~ 5 Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine. The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

~~**14 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~~

~~15~~ 6. Was the infant intubated or extubated on this day?
If Yes, Complete ~~Section B and/or Section C of~~ the SUPP05A

10.3 ~~2.2 Section B~~. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question ~~15~~ 6 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete a new report ~~Section B~~ for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on ~~Section B of~~ the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

~~**Section B**~~
~~1.~~3 Was the infant intubated on this day?
Record Yes if the infant was intubated on this day.
If Yes,
a. ~~If Yes~~, Record the time of intubation:
b. Record the following information prior to intubation:

1. Were blood gases obtained within 6 hours prior to the event?
~~Record~~ Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event. ~~, record ""~~*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
~~2.~~ **b. PCO_2**

~~3~~**2. FiO_2**
~~4~~**3. Saturation**
~~5~~**4. Apnea?** Record Yes if the infant had Apnea on this day.
~~6~~**5. Sepsis/R/O Sepsis?** Record Yes if the infant had Sepsis/R./O Sepsis on this day.
~~7~~**6. Hemodynamic instability?** Record Yes if the infant had hemodynamic instability on this day.
~~8~~**7. Clinically significant PDA?** Record Yes if the infant had clinically significant PDA on this day.
~~9~~**8. Other (specify).** Record Yes if the infant had other conditions this day. Specify these.

~~2~~4. Was the infant extubated on this day?

Record Yes if the infant was extubated on this day.

If Yes,

a. ~~If Yes,~~ Record the time of intubation:

b. Type of extubation:
   1= Planned
   2= Accidental

c. Record the following prior to extubation

1. Were blood gases obtained within 6 hours prior to the event?

~~Record~~ Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event. ~~; record ""~~*

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:

~~1~~a. pH

~~2~~b. PCO_2

~~3~~2. FiO_2

~~4~~3. Saturation

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. Episode Number

Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. Date Oximeter Replaced

Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. Time Oximeter Replaced

Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. Replacement Oximeter Serial Number

Record the six digit serial number of the replacement oximeter used.

e. Replacement Oximeter Color Code

Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

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.
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
~~10~~99= 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.**~~ Record a consecutive Report Number in the header for each form submitted. 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)[1]
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 Kris Zaterka-Baxter 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 or withdrawn (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.

   - **Withdrawn form study**
     Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations
  (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337(b) (6)

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

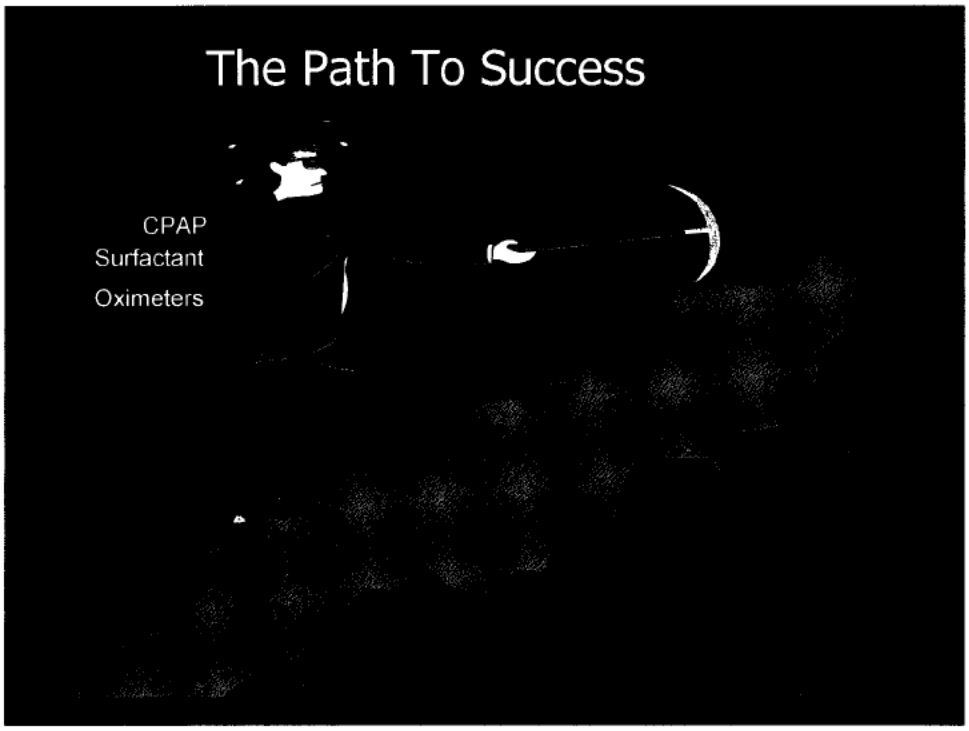
Signature of person explaining and getting consent DATE

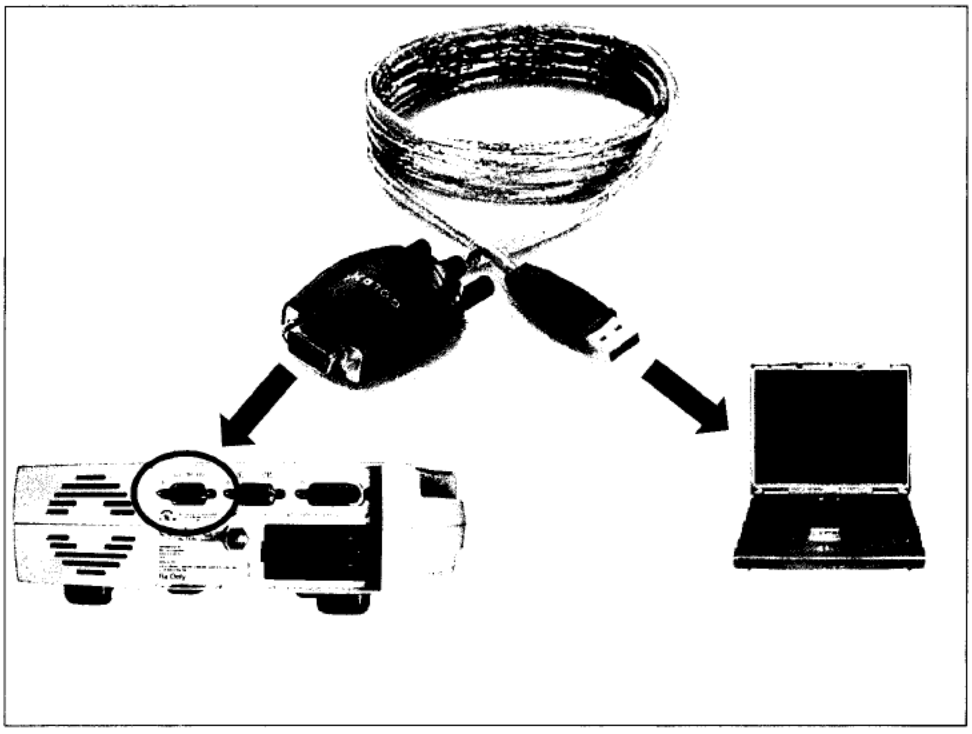
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

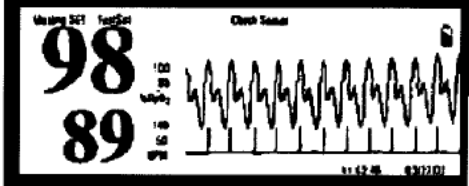
Use arrow key to select "Binary".

Select button.

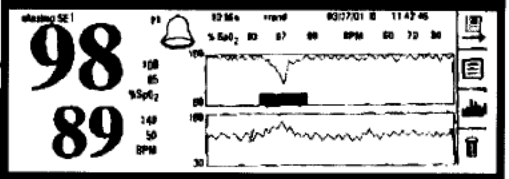
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

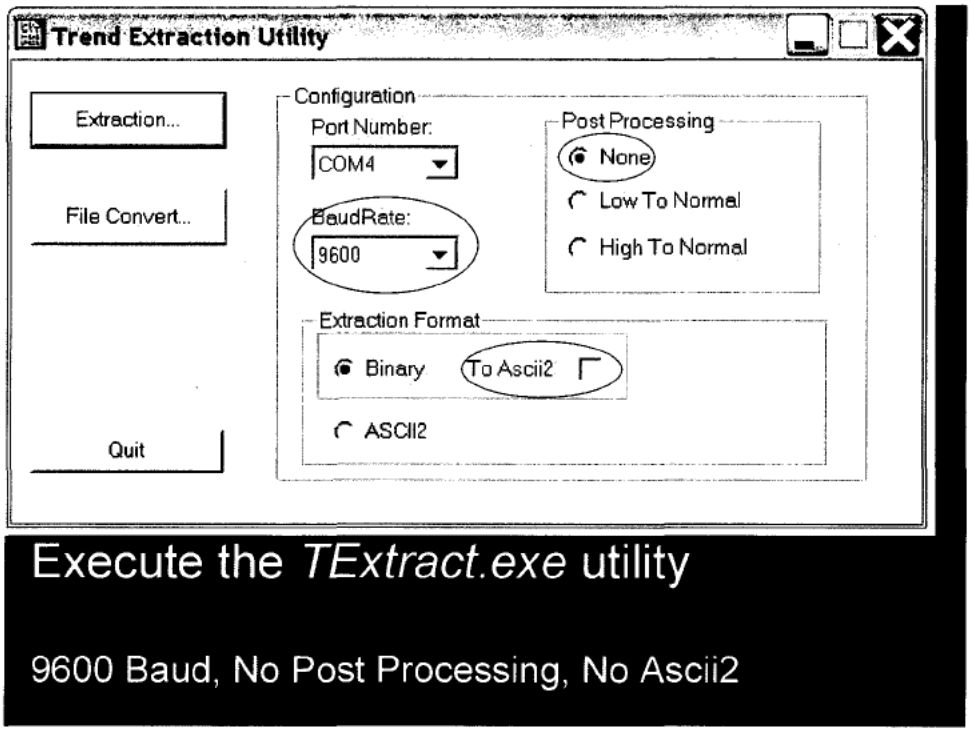
Make sure the Radical is in run mode and not in mode.



YES

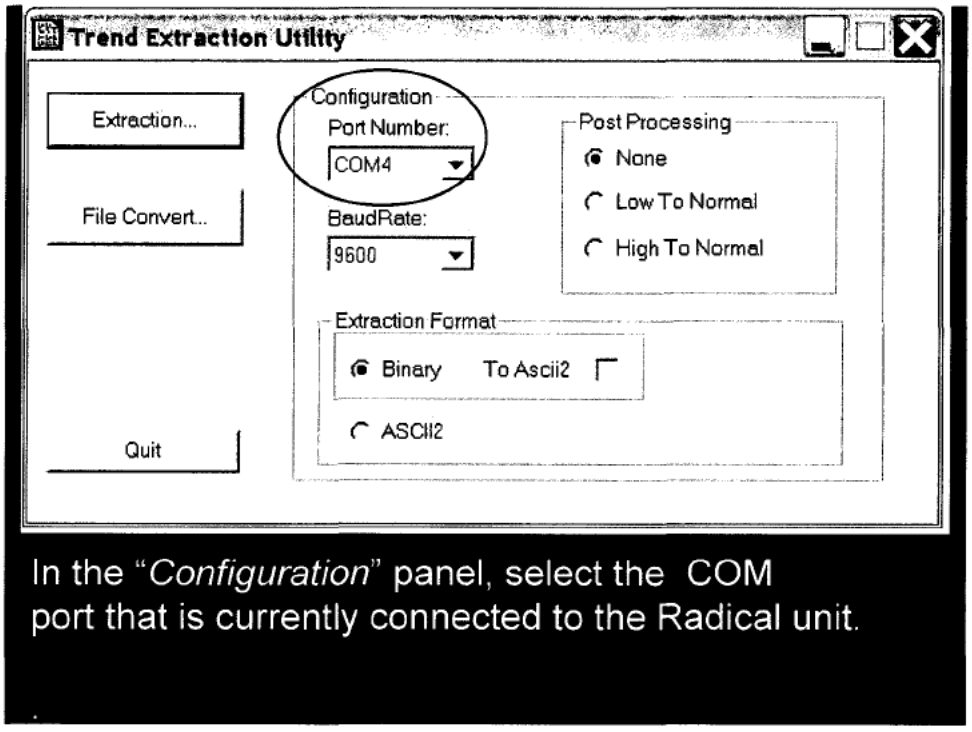


No

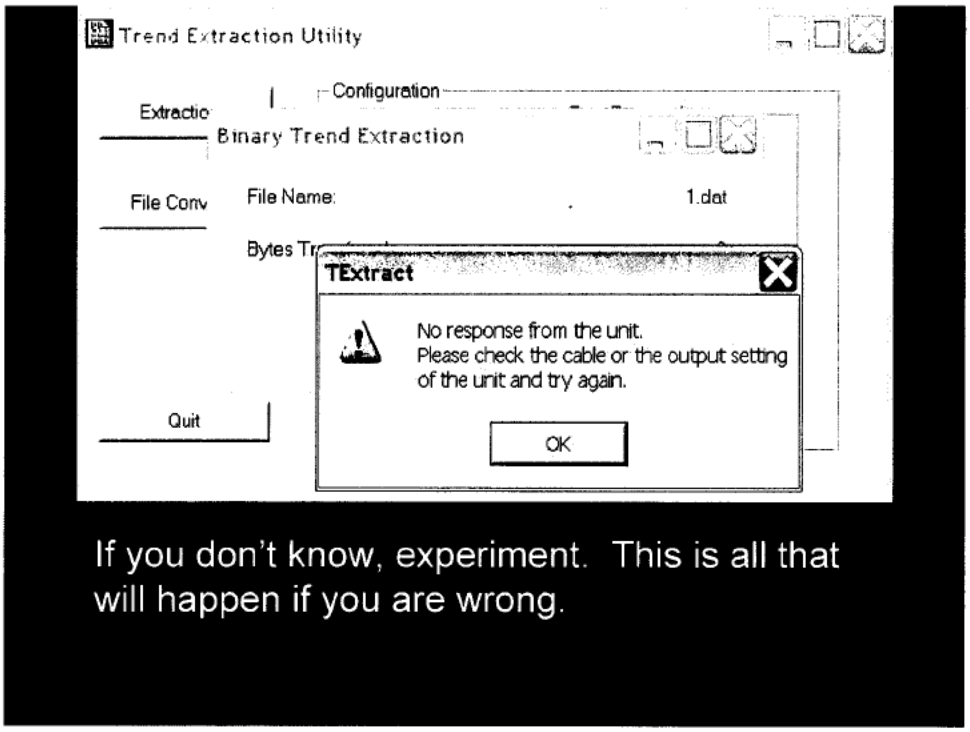


Execute the *TExtract.exe* utility

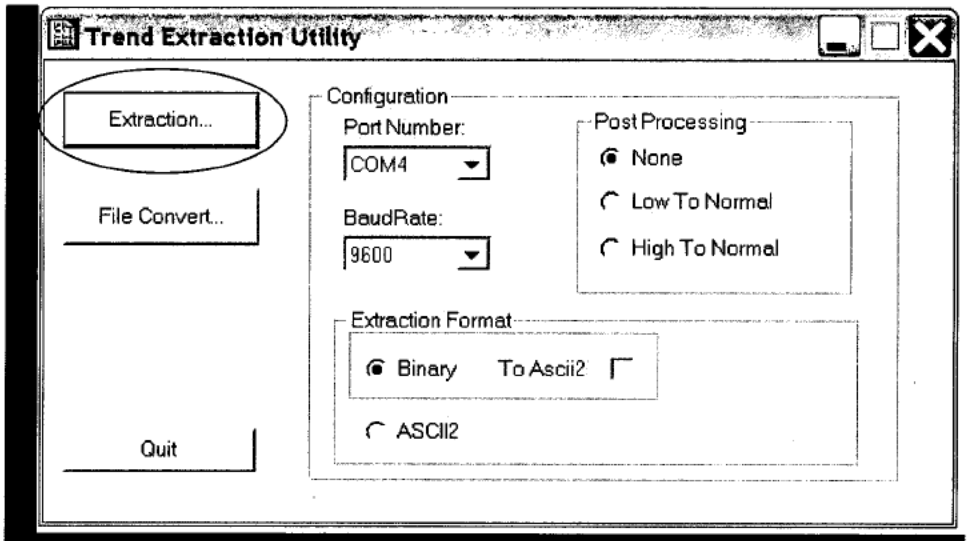
9600 Baud, No Post Processing, No Ascii2



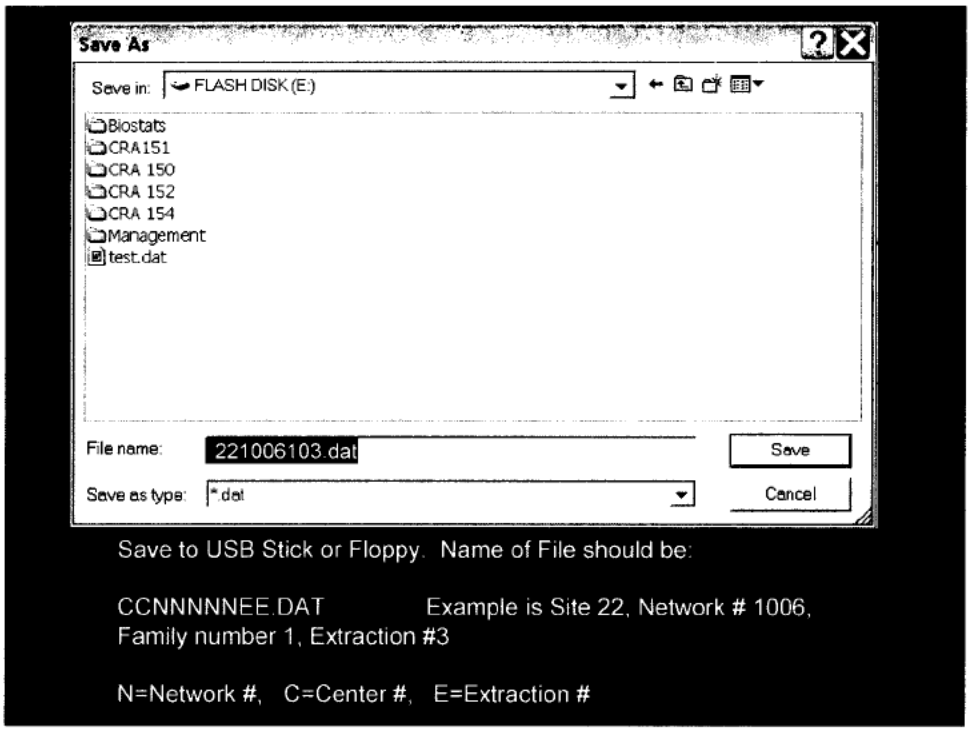
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

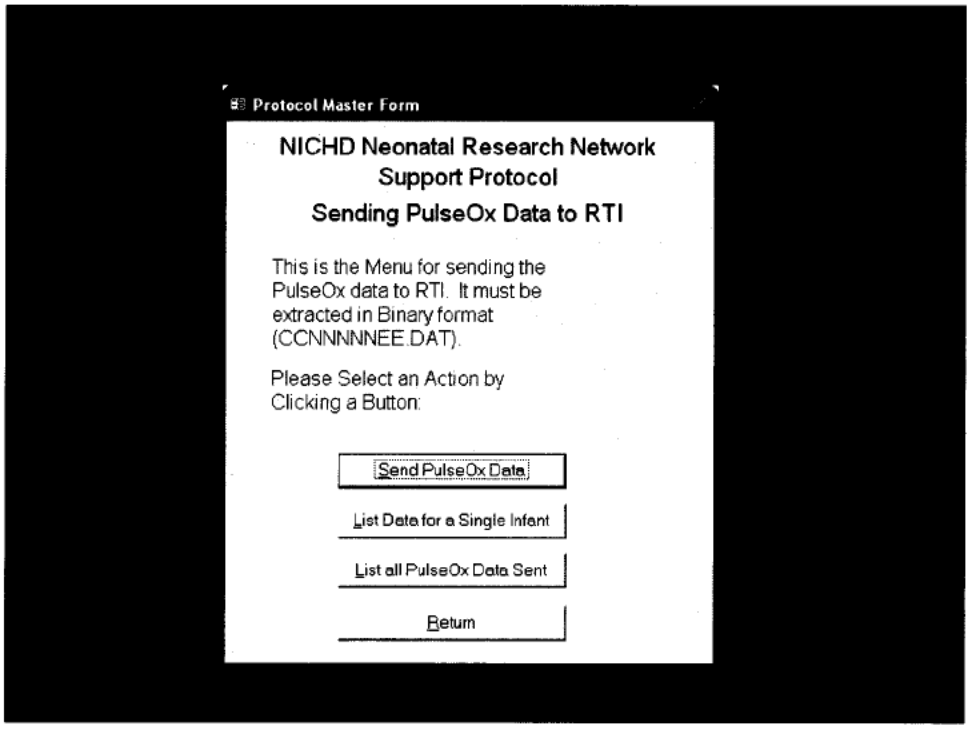


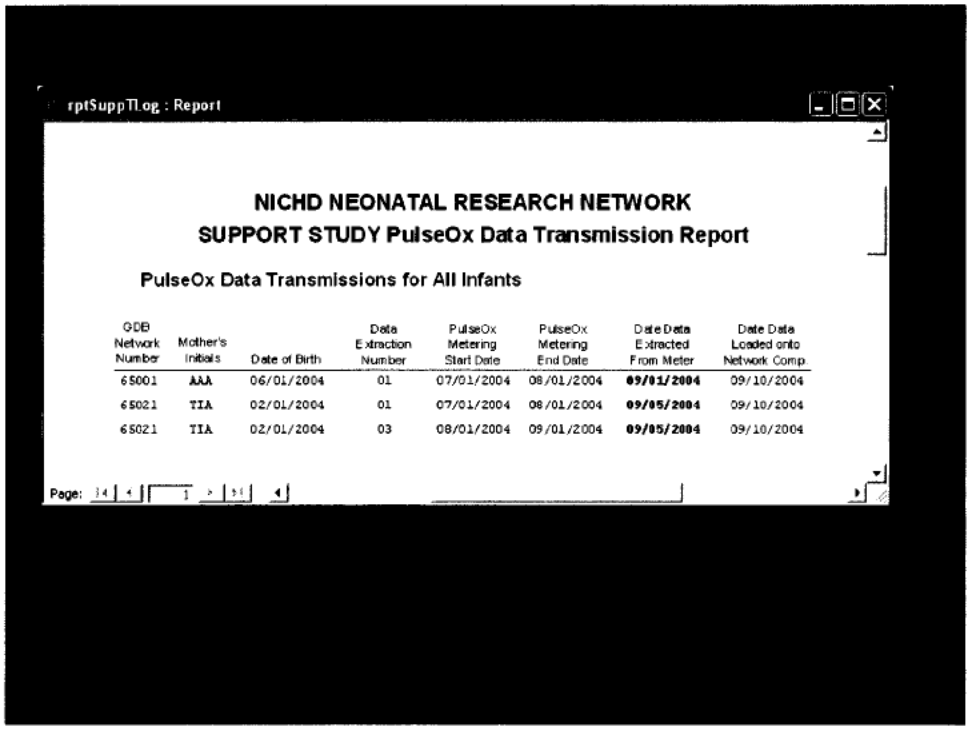
If you don't know, experiment. This is all that will happen if you are wrong.

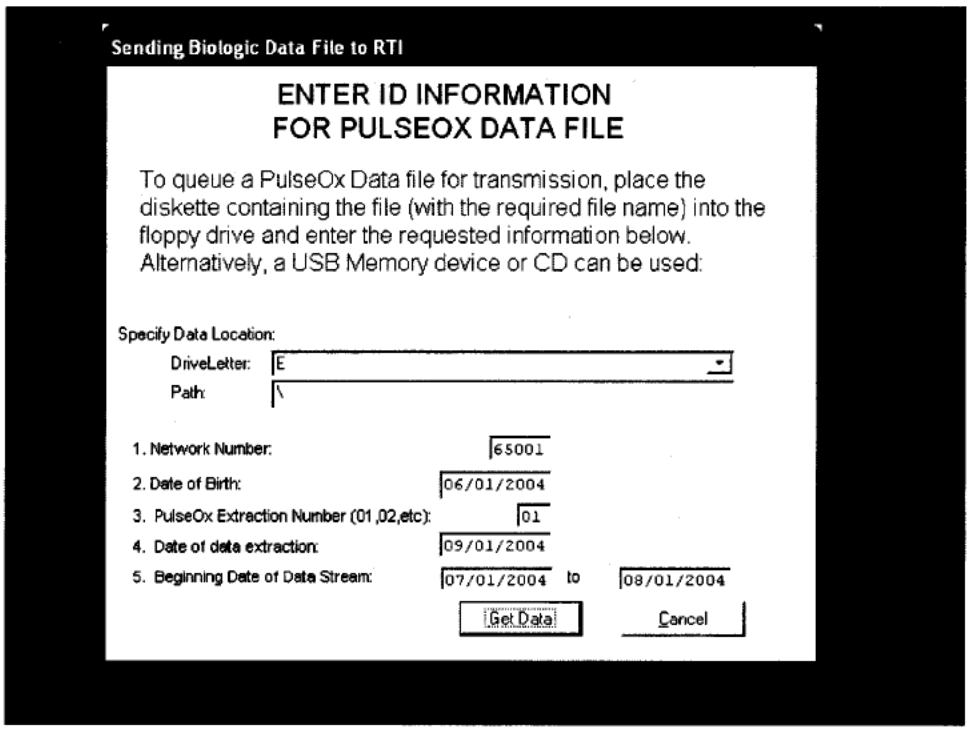


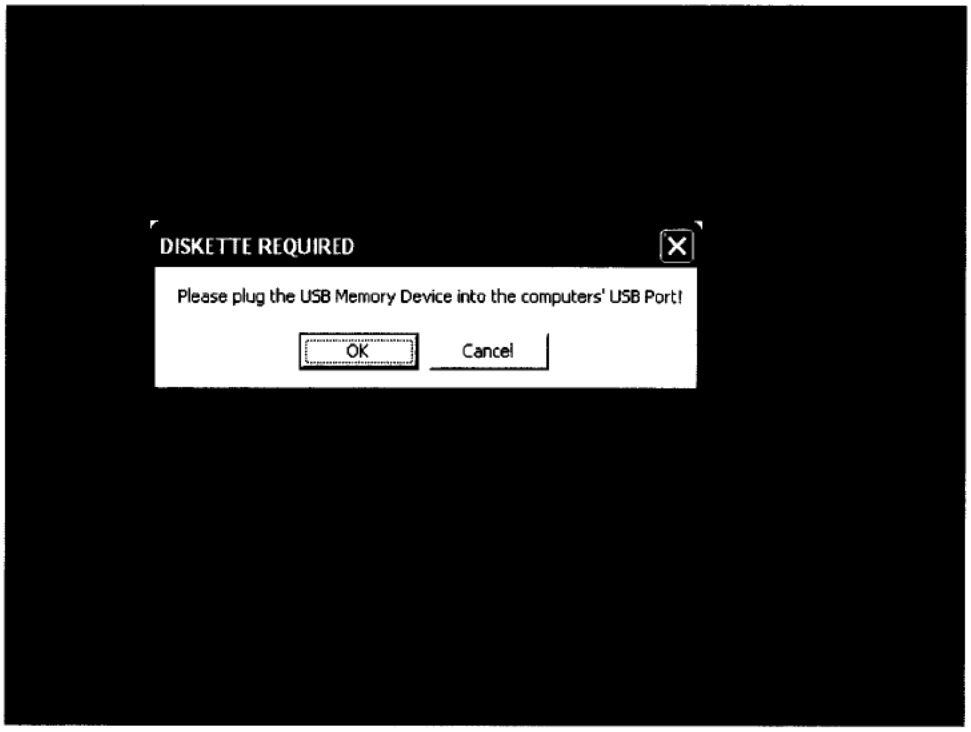
Hit Extraction.

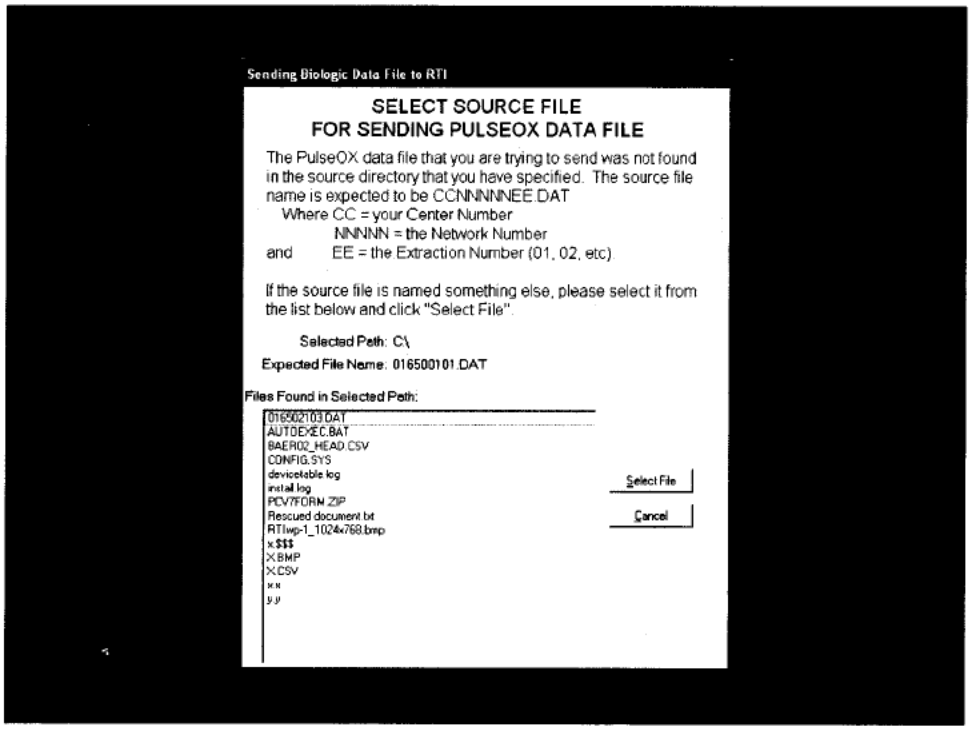


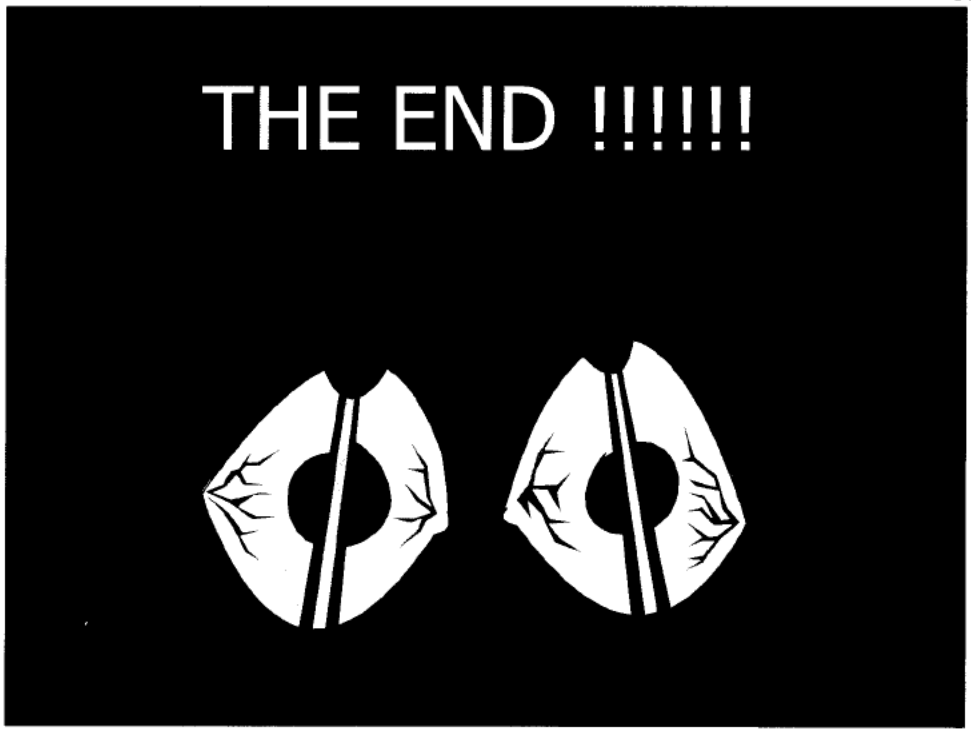












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

xxxx

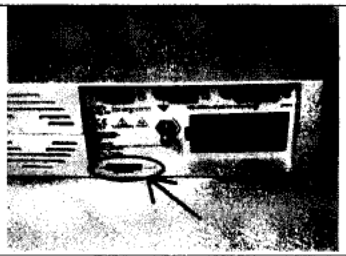
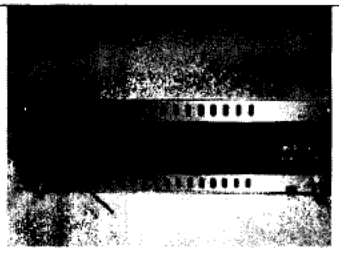
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?

   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006
Revised November 1, 2006

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 each time an intubation/extubation occurs after admission to the NICU through day of life 14.

Replacement Oximeter Form (SUPP05B)
This form is to be completed each time a study oximeter is replaced from study initiation to 36 weeks or status (whichever comes first).

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.

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, death or withdrawn (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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, 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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. Any subsequent extubations will also follow standard practice.

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 $Sa0_2$ ≥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?

Note: Complete this question only if question B.1 = YES

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
SUPP05 SUPP05A SUPP05B

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

1. Study Day: Enter the day this form is being completed.

2. Date: Enter the date that corresponds to the Study Day.

3. FiO2 Information: Record FiO2 and respiratory support closest to the Scheduled Time.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured
Record the actual time that the FiO2 was obtained based on a 24-hour clock. This time should be recorded adjacent to the closed Scheduled Time listed in column "a".

f. FiO_2
Record the FiO_2 at the scheduled time points. When a blood gas is obtained during a scheduled time, record the FiO2 corresponding to that blood gas. This will be the same FiO2 recorded in question 4 (f) and will supersede the blood gas obtained q2hrs.

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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

4. Blood Gas Information: Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59 if available.

a. Scheduled Time
The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 08:00
2. Scheduled Time: 16:00
3. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one.

c. pH
Record the acid base status of the blood.
d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** corresponding to the blood gas at the scheduled time points. Record this FiO2 in question 3 "f" at the appropriate time measured.

g. Source:
Record the source of the blood gas
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
9= No Support all day and off Study oximeter

i. If Mode = 5 record Flow Rate
Record the flow rate for infants on nasal cannula

j. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

5. Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine. The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

6. Was the infant intubated or extubated on this day?
If Yes, Complete the SUPP05A

10.3 Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 6 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete a new report for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

3 Was the infant intubated on this day?
Record Yes if the infant was intubated on this day.
If Yes,
a. Record the time of intubation:
b. Record the following information prior to intubation:

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation
4. Apnea? Record Yes if the infant had Apnea on this day.
5. Sepsis/R/O Sepsis? Record Yes if the infant had Sepsis/R./O Sepsis on this day.
6. Hemodynamic instability? Record Yes if the infant had hemodynamic instability on this day.
7. Clinically significant PDA? Record Yes if the infant had clinically significant PDA on this day.
8. Other (specify). Record Yes if the infant had other conditions this day. Specify these.

4. Was the infant extubated on this day?
Record Yes if the infant was extubated on this day.

If Yes,
a. Record the time of intubation:

b. Type of extubation:
1= Planned
2= Accidental

c. Record the following prior to extubation

1. Were blood gases obtained within 6 hours prior to the event?
Code 'Yes' if the blood gas that, in the opinion of the investigator, is most associated with the event was obtained within 6 hours prior to the event. Record 'No' if there is no blood gas measurement associated with this event or was obtained >6 hours prior to the event.

Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code 'No'.

If Yes, record:
a. pH
b. PCO_2

2. FiO_2
3. Saturation

10.4 Instructions for completing the Replacement Oximeter Form (SUPP05B)

The purpose of this form is to record each time a study oximeter is replaced on an infant from study initiation to 36 weeks or status (whichever comes first).

a. Episode Number
Consecutively record each oximeter replacement as indicated by the preprinted episode number

b. Date Oximeter Replaced
Record the date the replacement oximeter was first utilized for this infant in MM/DD/YYYY format

c. Time Oximeter Replaced
Record the time the replacement oximeter was first utilized for this infant based on a 24-hour clock

d. Replacement Oximeter Serial Number
Record the six digit serial number of the replacement oximeter used.

e. Replacement Oximeter Color Code
Record the color code assigned to the replacement oximeter.
1= Blue
2= Orange

Note: Color codes are assigned by RTI when study oximeters are sent to participating Centers. Please contact RTI study coordinator at 919-485-7750, zaterka@rti.org to verify color code assignments if in question.

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.
11= Infant randomized to incorrect gestational age group
12= Postnatal steroids given for BPD/CLD within 21 days of life
99= 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:**

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 Record a consecutive Report Number in the header for each form submitted. This form should be completed and keyed at the sites as soon as possible.

1. Air leak
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[1]
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 Kris Zaterka-Baxter 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, death or withdrawn (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.

   - **Withdrawn form study**
     Record '6' if the infant was withdrawn from study by a parent, legal guardian or physician; Use the F5 key to comment on circumstances of withdrawal if known (i.e., parent or physician withdrawal)

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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b)

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

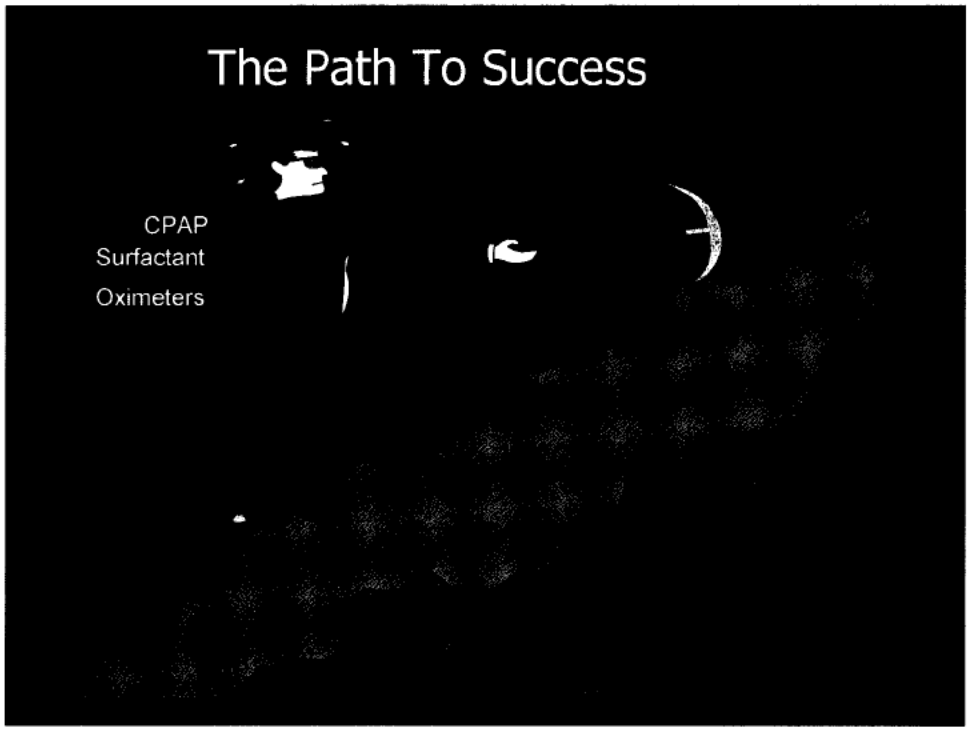
Signature of person explaining and getting consent DATE

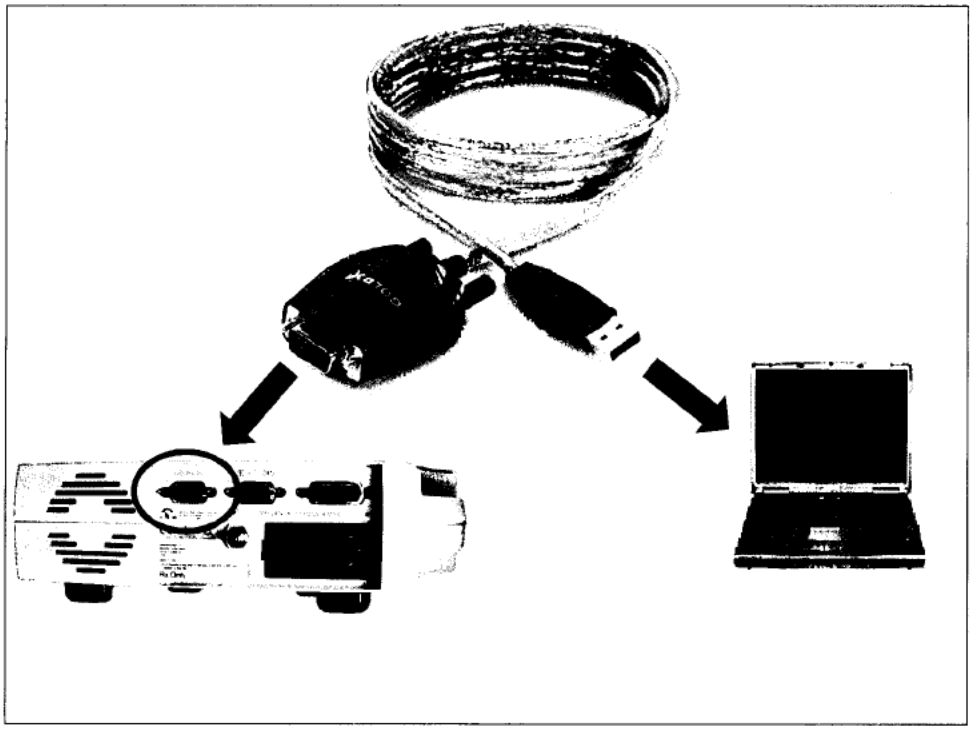
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

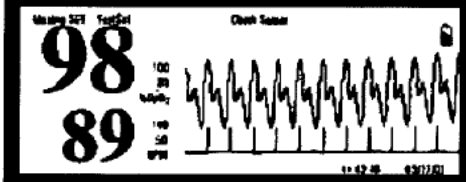
Use arrow key to select "Binary".

Select button.

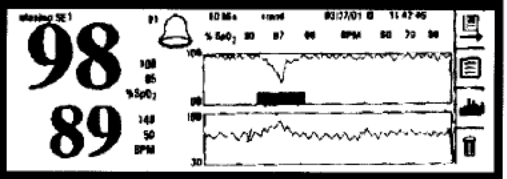
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

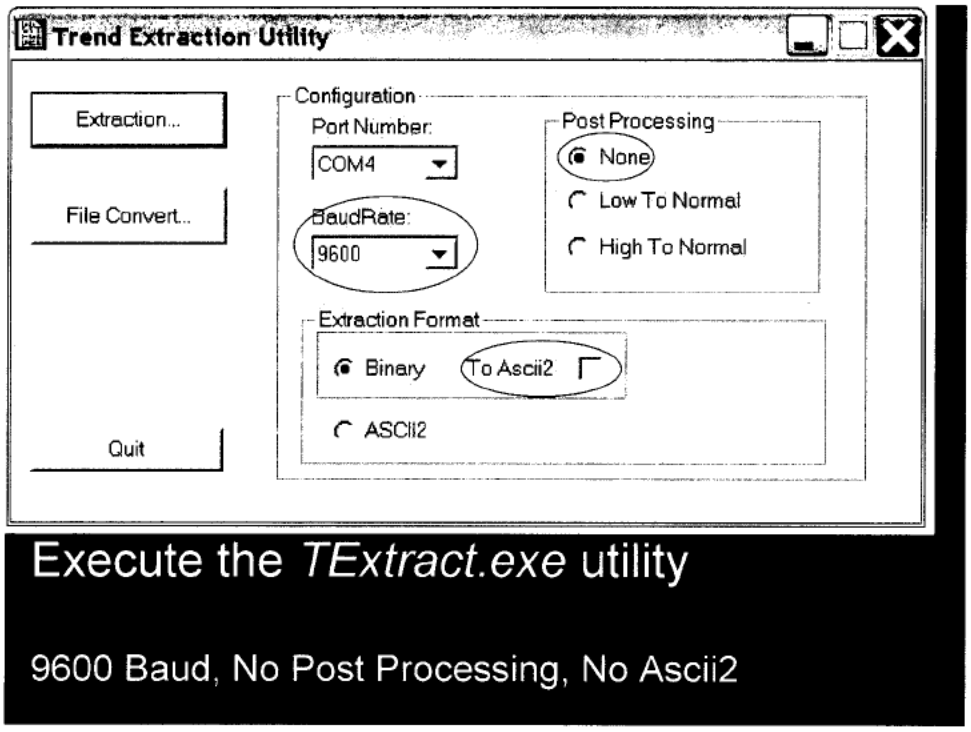
Make sure the Radical is in run mode and not in mode.



YES

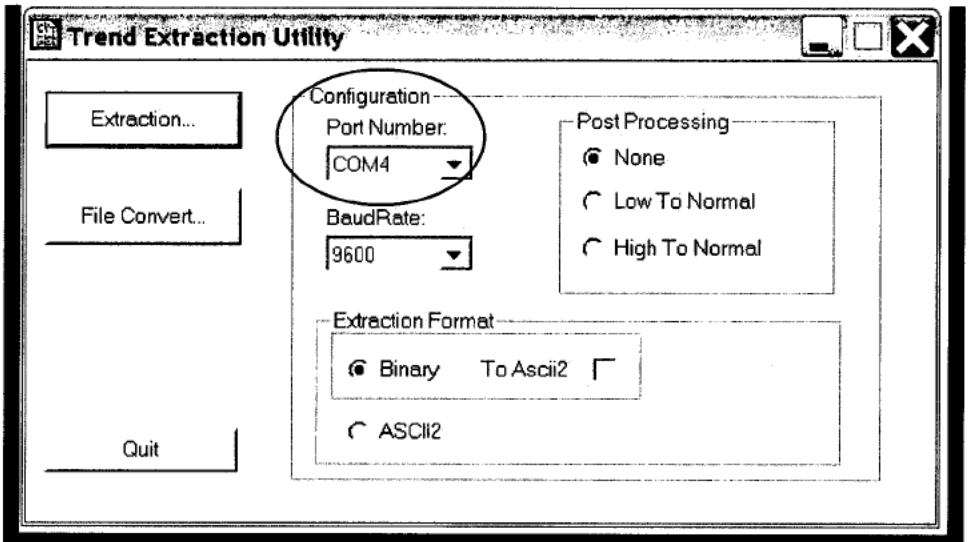


No

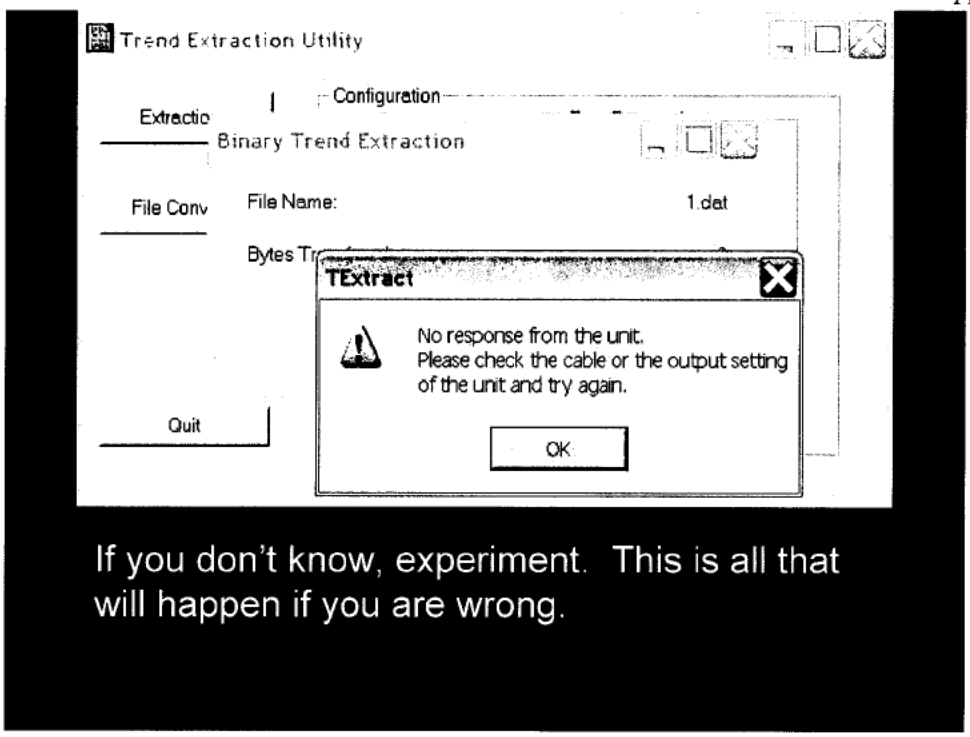


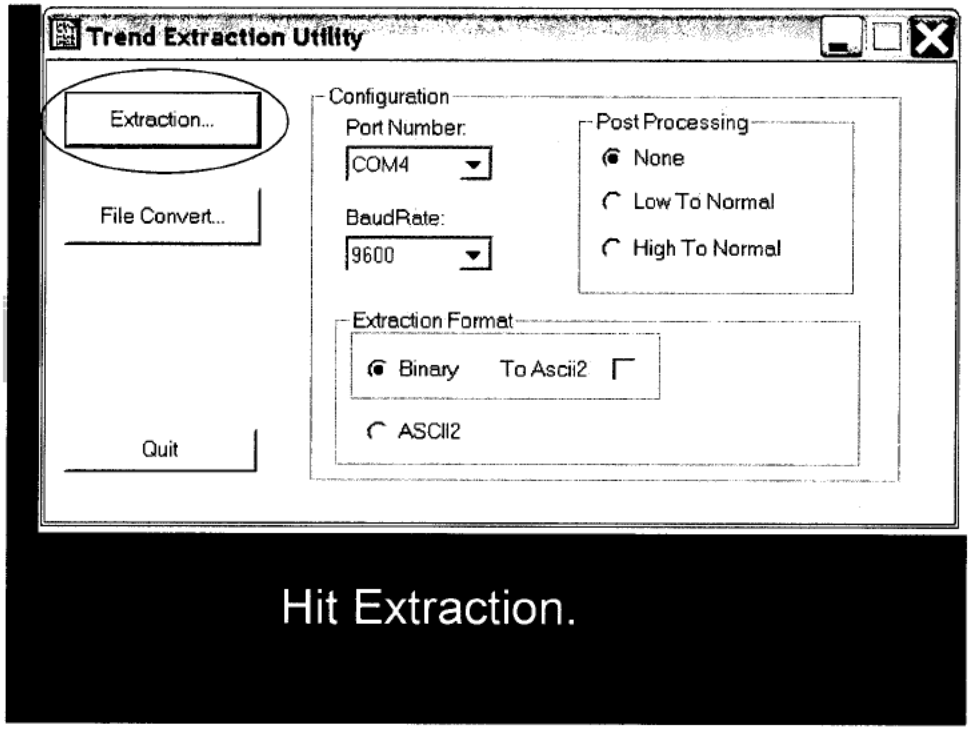
Execute the *TExtract.exe* utility

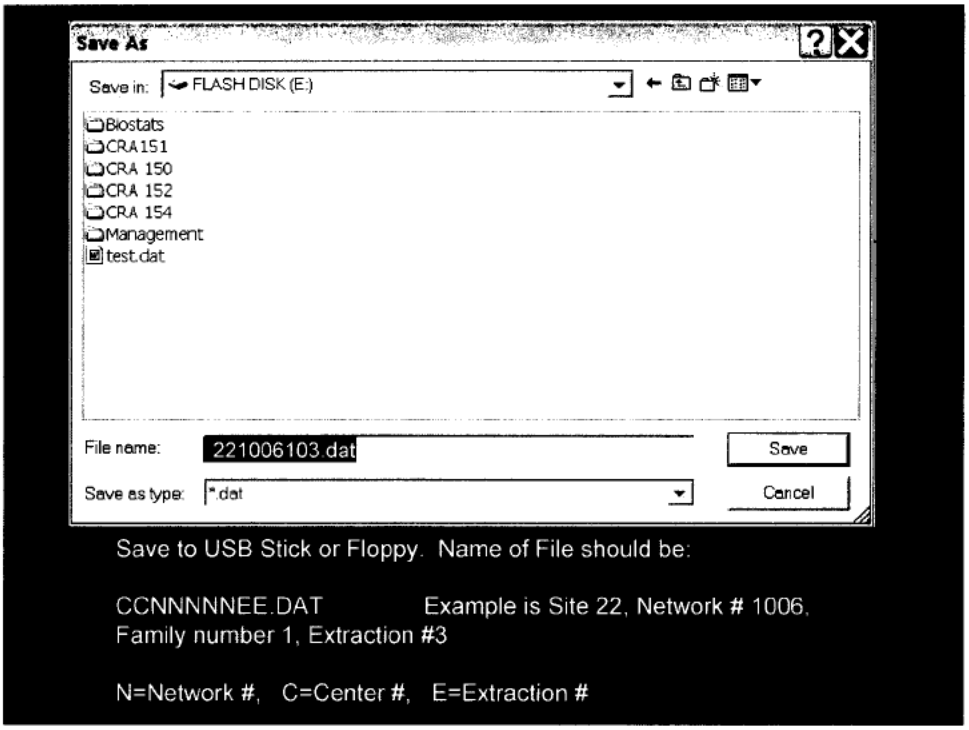
9600 Baud, No Post Processing, No Ascii2

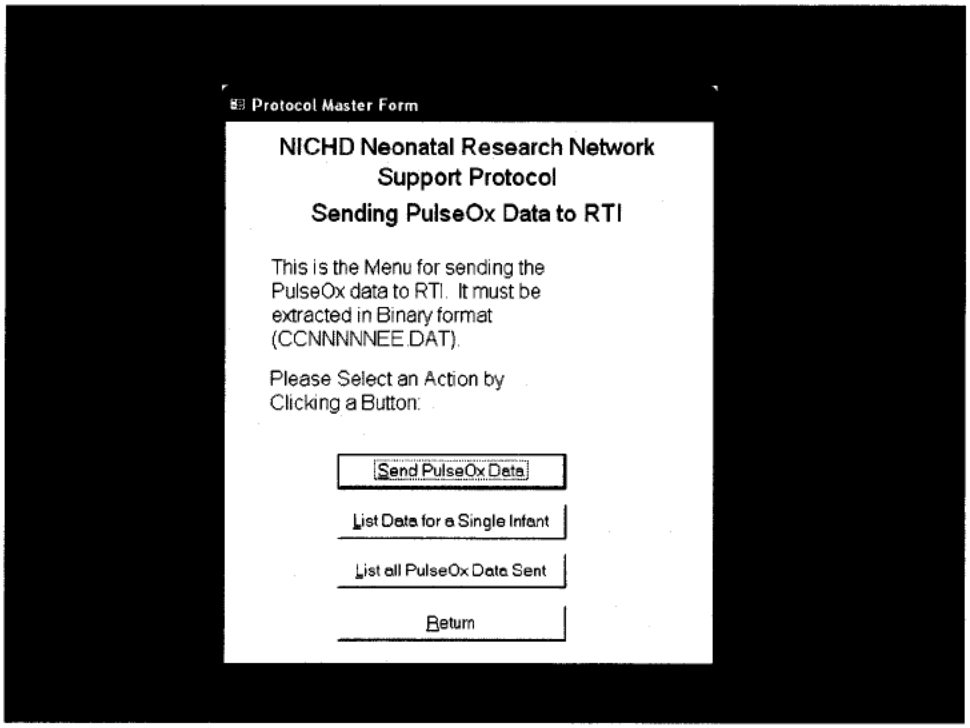


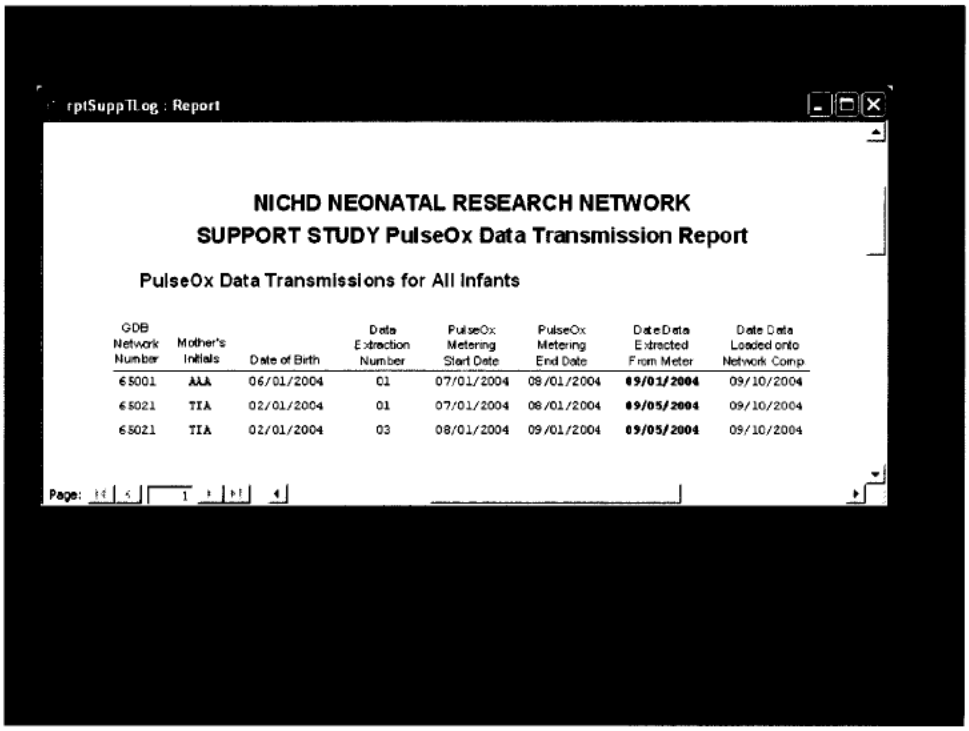
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

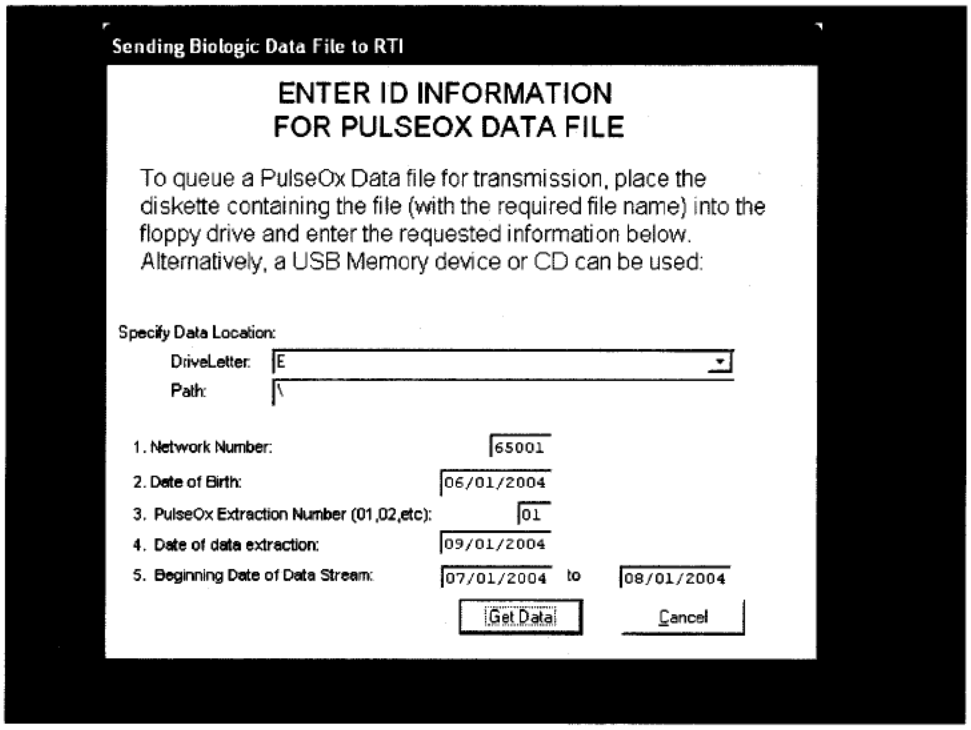


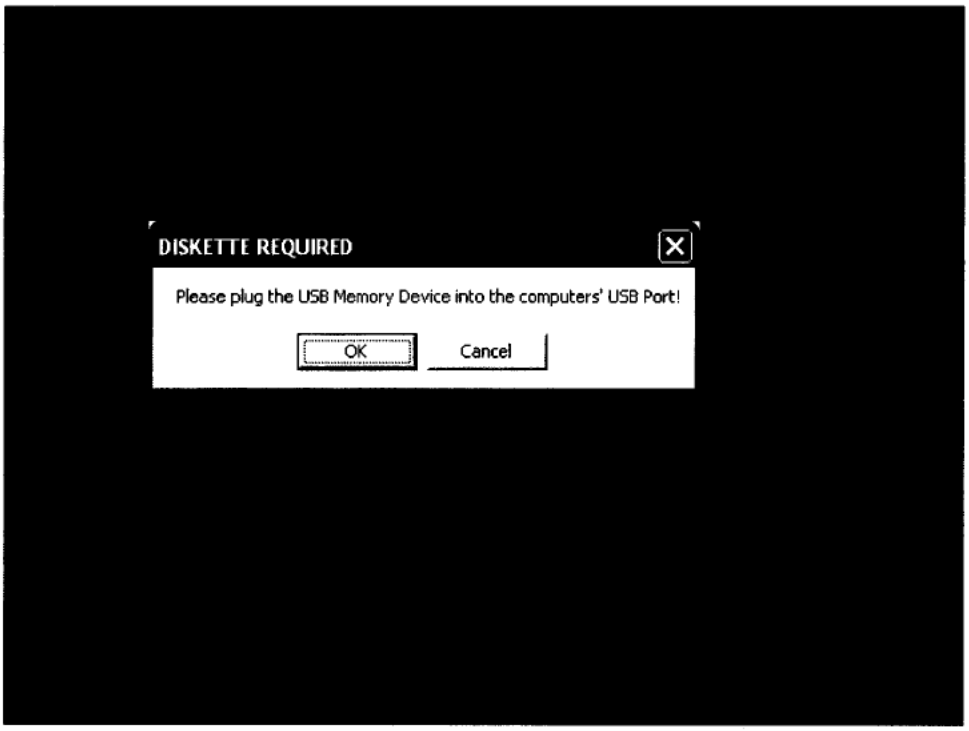


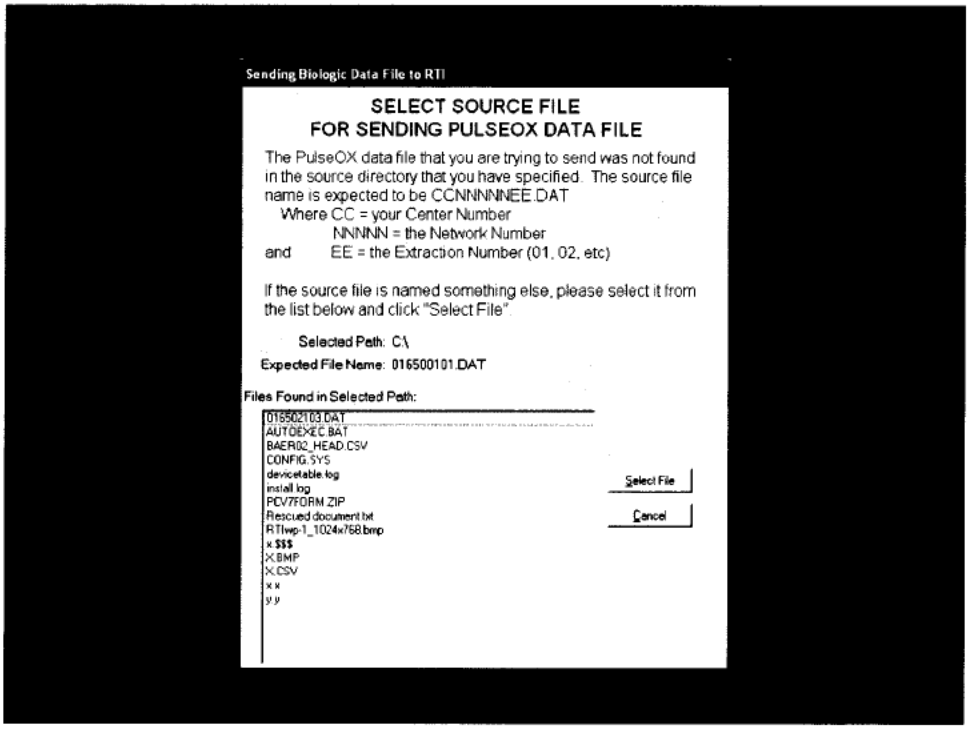


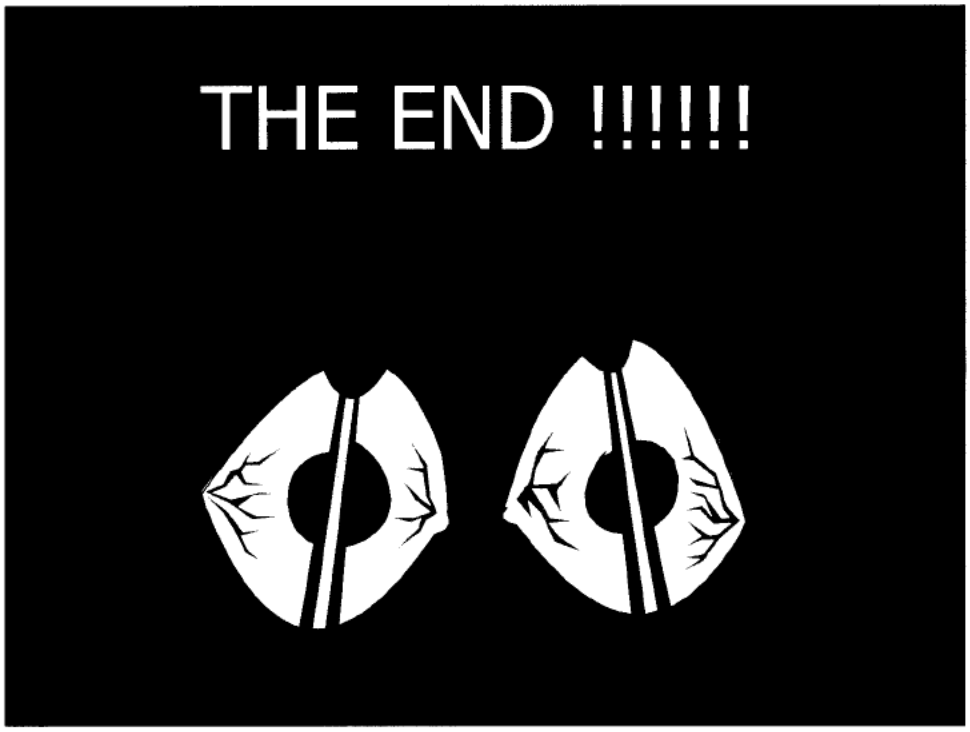












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

 # xxxx

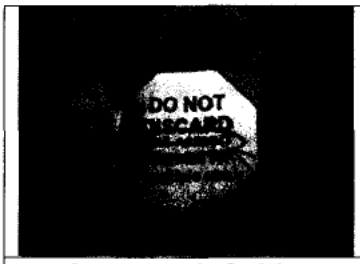
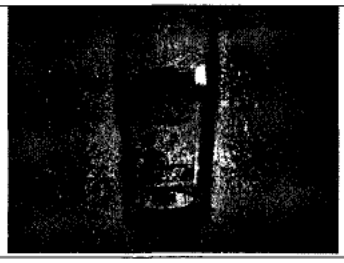
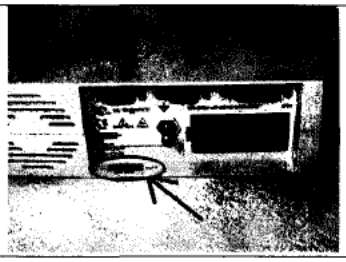
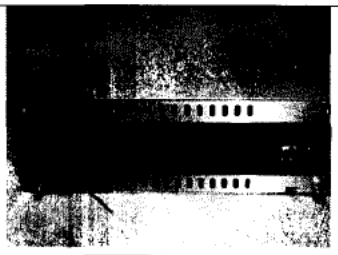
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
     (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
   Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
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 ≥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
   Complete this question only if Q.B.1 = YES
   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: __ __ __

Complete a form each day through DOL 14 **1. Study Day:** __ __ **2. Date:** __ __ / __ __ / __ __ __ __.

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
2. 04 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
3. 06 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
4. 08 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
5. 10 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
6. 12 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
7. 14 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
8. 16 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
9. 18 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
10. 20 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
11. 22 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
12. 23 : 59	__ __ : __ __	__. __ __	___	__. __ __ __	___

5. Oximeter Alarm Checks Q6hr/day

a. __ __ : __ __

b. __ __ : __ __

c. __ __ : __ __

d. __ __ : __ __

6. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

4. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 08 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
2. 16 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
3. 23 : 59	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___

*Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

DRAFT

SUPP05A version 4.0
Revised June 5, 2006
Revised November 1, 2006

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Report ~~This form should be completed~~ each time an intubation/extubation occurs after admission to the NICU through DOL 14, ~~in the same day.~~ Number each event sequentially.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
   If yes

   a. Record the time of intubation __ __ : __ __ (Hr : Min)

   b. Record the following prior to intubation :
      1. Were blood gases obtained within 6 hours prior to the event? Y N
         If yes,
         a. pH __. __ __
         b. PCO_2 __ __ __
      2. FiO_2 __. __ __
      3. Saturation __ __ __
      4. Apnea? Y N
      5. Sepsis/R/O Sepsis? Y N
      6. Hemodynamic instability? Y N
      7. Clinically significant PDA? Y N
      8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
   If Yes,

   a. Record the time of extubation __ __ : __ __ (Hr : Min)

   b. Type of extubation: __

1= Planned	2= Accidental

   c. Record the following prior to extubation
      1. Were blood gases obtained within 6 hours prior to the event? Y N
         If yes,
         a. pH __. __ __
         b. PCO_2 __ __ __
      2. FiO_2 __. __ __
      3. Saturation __ __ __

Initials of person completing this form: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N
   If yes

   a. Record the time of intubation __ __ : __ __ (Hr : Min)

   b. Record the following prior to intubation :
      1. Were blood gases obtained within 6 hours prior to the event? Y N
         If yes,
         a. pH __. __ __
         b. PCO_2 __ __ __
      2. FiO_2 __. __ __
      3. Saturation __ __ __
      4. Apnea? Y N
      5. Sepsis/R/O Sepsis? Y N
      6. Hemodynamic instability? Y N
      7. Clinically significant PDA? Y N
      8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N
   If Yes,

   a. Record the time of extubation __ __ : __ __ (Hr : Min)

   b. Type of extubation: __

1= Planned	2= Accidental

   c. Record the following prior to extubation
      1. Were blood gases obtained within 6 hours prior to the event? Y N
         If yes,
         a. pH __. __ __
         b. PCO_2 __ __ __
      2. FiO_2 __. __ __
      3. Saturation __ __ __

Initials of person completing this form: __ __ __

The SUrfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Replacement Oximeter Form

DRAFT

Center: ___ **Site:** ___ **Network No.** ___ ___ ___ ___ **Birth No.** ___ **Mother's Initials:** ___ ___ ___

Complete this form each time a study oximeter is replaced from study initiation to 36 weeks or status.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
2.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
3.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
4.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
5.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
6.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
7.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
8.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
9.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___
10.	___ ___ / ___ ___ / ___ ___ ___ ___	___ ___ : ___ ___	___ ___ ___ ___ ___ ___	___

PROTOCOL DEVIATION FORM
DRAFT

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)***~~

   11. Infant randomizes to incorrect gestational age group

   12. Postnatal steroids given for BPD/CLD within 21 days of life.

   99. 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: __ __ __

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: ___ ___ ___

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

OUTCOME STATUS FORM

SUPP09 version 2.1
January 4, 2005
Revised October 26, 2005
Revised November 1, 2006

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 or withdrawn (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	6 = Withdrawn from study

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: ___ ___ ___

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NRN DSMC meeting for Support
Date: Thursday, November 09, 2006 12:19:18 PM

Pease see additional info below.
Thanks,

Kris

From: Webb, Robin E.
Sent: Thursday, November 09, 2006 11:15 AM
To: Zaterka-Baxter, Kristin
Subject: FW: NRN DSMC meeting for Support

From: Kiley, James (NIH/NHLBI) [E] [mailto:kileyj@nhlbi.nih.gov]
Sent: Thursday, November 09, 2006 10:51 AM
To: Webb, Robin E.
Cc: Hunt, Carl (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: NRN DSMC meeting for Support

Robin:

Dr. Dorothy gail will replace Dr. Hunt as the NHLBI rep for this dsmc. PI contact her directly for scheduling and other issues. Thanks, Jim

-----Original Message-----
From: Hunt, Carl (NIH/NHLBI) [E]
Sent: Thursday, November 09, 2006 10:34 AM
To: 'Webb, Robin E.'
Cc: Kiley, James (NIH/NHLBI) [E]
Subject: RE: NRN DSMC meeting for Support

(b) (6) [redacted]. Since Dr. Kiley is intending to appoint a replacement for me on the DSMC, please contact him for further information. Thank you.
Dr. Hunt

-----Original Message-----
From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Thursday, November 09, 2006 9:58 AM
To: mikeross@ucla.edu; Hunt, Carl (NIH/NHLBI) [E]; mcallen@jhmi.edu
Subject: FW: NRN DSMC meeting for Support

Please let me know if you would be able to attend the Support meeting in DC on Tuesday, 2/6.

Thanks,
Robin

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Wednesday, November 01, 2006 2:35 PM
To: (b) (6) [redacted]; Boyle, Robert J *HS; cgleason@u.washington.edu; [SCRN] Willinger, Marian; tclemons@emmes.com; mikeross@ucla.edu; kant@unc.edu; huntc@nhlbi.nih.gov; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; Das, Abhik; higginsr@mail.nih.gov; Gantz, Marie
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject: NRN DSMC meeting for Support

We were unable to come up with a day that worked for everyone for the Support study DSMC meeting to review the first planned interim analysis that will be taking place in the DC area. Please let me know which of the days listed below you are available. The meeting will be for one day from ~ 8:30 to 3:30pm.

Thanks,

Robin

Mon 2/5/07

Tues 2/6

Fri 2/9

Mon 2/12

Tues 2/13

Wed 2/14

Thurs 2/15

Fri 2/16

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NRN DSMC meeting for Support
Date: Thursday, November 09, 2006 12:18:35 PM

Just FYI, please see below.
Thanks,

Kris
-----Original Message-----
From: Webb, Robin E.
Sent: Thursday, November 09, 2006 11:12 AM
To: Zaterka-Baxter, Kristin
Subject: FW: NRN DSMC meeting for Support

FYI

-----Original Message-----
From: Hunt, Carl (NIH/NHLBI) [E] [mailto:huntc@nhlbi.nih.gov]
Sent: Thursday, November 09, 2006 10:34 AM
To: Webb, Robin E.
Cc: Kiley, James (NIH/NHLBI) [E]
Subject: RE: NRN DSMC meeting for Support

(b) (6) [redacted]

Since Dr. Kiley is intending to appoint a replacement for me on the DSMC, please contact him for further information. Thank you.
Dr. Hunt

-----Original Message-----
From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Thursday, November 09, 2006 9:58 AM
To: mikeross@ucla.edu; Hunt, Carl (NIH/NHLBI) [E]; mcallen@jhmi.edu
Subject: FW: NRN DSMC meeting for Support

Please let me know if you would be able to attend the Support meeting in DC on Tuesday, 2/6.

Thanks,
Robin

From: Webb, Robin E. [mailto:rwebb@rti.org]
Sent: Wednesday, November 01, 2006 2:35 PM
To: (b) (6) [redacted]; Boyle, Robert J *HS; cgleason@u.washington.edu; [SCRN] Willinger, Marian; tclemons@emmes.com; mikeross@ucla.edu; kant@unc.edu; huntc@nhlbi.nih.gov; merran.thomson@ic.ac.uk; mcallen@jhmi.edu; Das, Abhik; higginsr@mail.nih.gov; Gantz, Marie
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject: NRN DSMC meeting for Support

We were unable to come up with a day that worked for everyone for the Support study DSMC meeting to review the first planned interim analysis that will be taking place in the DC area. Please let me know which of the days listed below you are available. The meeting will be for one day from ~ 8:30 to 3:30pm.

Thanks,

Robin

Mon 2/5/07

Tues 2/6

Fri 2/9

Mon 2/12

Tues 2/13

Wed 2/14

Thurs 2/15

Fri 2/16

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT DSMC
Date: Thursday, November 09, 2006 11:49:01 AM

Nope

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Sent: Thu Nov 09 11:37:21 2006
Subject: SUPPORT DSMC

Cathy

Carl Hunt (b) (6) . Dorothy Gail from NHLBI will sit in at the next DSMC meeting as their program rep. DO I need to do anything formal for this?
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: Bradley Yoder
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: SUPPORT adverse events
Date: Wednesday, November 08, 2006 1:25:56 PM
Attachments: Stopping Rules Feb 28 2005.doc

Hi Brad
We used the occurrence of death in the first 14 days as a monitoring issue. We cannot get the actual deaths for the infants enrolled in the study as death is a primary outcome and RTI will not provide this as expected. However the stopping rules document has the occurrence of death in the first 14 days by gestational strata and overall. I think that you could quote these figures as the expected mortality by strata.
I have attached that document
Let me know if this will work
Be well
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Wednesday, November 08, 2006 9:24 AM
To: Neil Finer
Cc: higginsr@mail.nih.gov
Subject: SUPPORT adverse events

Neil:
One of our SUPPORT babies died 2nd severe RDS/PPHN/anuria related to twin-twin transfusion.
One of the questions the IRB adverse event forms asks is "What is the frequency of this event in the entire study population?"
I cannot find death as a measurment in any of the Adverse Event reports that have been sent out.
Do you have a number I can give them??

Thanks.

Brad

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: Webb, Robin E.
To: Webb, Robin E.; nfiner@ucsd.edu; wrich@ucsd.edu; Gantz, Marie; Auman, Jeanette O.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin
Cc: fmartinez@ucsd.edu
Subject: RE: Support monitoring conf call
Date: Tuesday, November 07, 2006 3:32:53 PM

The call to discuss site monitoring procedures and logistics for the Support study has been scheduled for:

Thursday, November 9
1:00pm ET

Dial:
Outside the USA
1-203-310(b) (6)
or
Within the USA
866-675-(b) (6)

Then, enter Participant Passcode:
(b) (6)

From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Support monitoring conf call
Date: Tuesday, November 07, 2006 11:32:39 AM
Attachments: Monitoring SOP draft20061102.doc
Monitor Report20061102.doc
Importance: High

Hey Rose,

Are you available Thurs 11/9 between 12-2pm ET for this call? If not, please let me know your availability for the other days below.

Thanks,
Robin

From: Webb, Robin E.
Sent: Monday, November 06, 2006 9:41 AM
To: 'nfiner@ucsd.edu'; 'wrich@ucsd.edu'; Gantz, Marie; Auman, Jeanette O.; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Zaterka-Baxter, Kristin
Cc: Webb, Robin E.; 'fmartinez@ucsd.edu'
Subject: FW: Support monitoring conf call
Importance: High

We need to schedule a call to discuss site monitoring procedures and logistics for the Support study. Attached are the documents for the call. Please let me know your availability for the days listed below.

Thanks,
Robin

Thurs 11/9
Fri 11/10

Mon 11/13
Tues 11/14
Wed 11/15
Thurs 11/16
Fri 11/17

1. MONITORING

As the sponsor of US federally funded clinical research, the National Institute of Child Health and Development (NICHD) has a regulatory responsibility for oversight of all Neonatal Research Network (NRN) trials. The purposes of monitoring a research study are to verify that:

- the rights and well-being of human subjects are protected
- the reported trial data are attributable, legible, contemporaneous, original, accurate, and verifiable from source documents
- the conduct of the trial is in compliance with the currently approved protocol/amendment, and the applicable regulatory requirements

1.1 Clinical Site Monitoring Group

In keeping with this regulatory oversight obligation, NICHD has delegated the responsibility for on-site monitoring to Research Triangle Institute International (RTI), which serves as the Data Coordinating Center (DCC) for the NRN under cooperative agreement with the NICHD.

1.2 Clinical Site Monitoring Objectives

The DCC for the NRN will conduct periodic on-site monitoring visits to academic medical centers where NRN clinical research takes place,. The objectives of such visits will include monitoring and reporting subsequent findings in the following general areas:

- perform source document verification to ensure the accuracy and completeness of trial data
- review data safety and confidentiality issues related to handling and keying of data forms and subsequent data transmission to the DCC
- review informed consent forms, procedures, and documentation
- identify problems with protocol compliance relative to protocol procedures, and all applicable regulatory requirements.
- verify the proper storage, dispensing, and accountability of study products under investigation, when applicable
- document the implementation of appropriate internal site quality control and quality assurance procedures, as applicable
- assess the need for additional site personnel training and additional staff

1.2.1 Site Monitoring Visits

Site monitoring visits will be conducted on a regular basis (usually quarterly) for approximately two days per visit. The monitoring schedule may vary depending on the nature of the studies being conducted by the NRN at any given point in time. Monitors from the DCC will contact site staff in advance to schedule the monitoring visits. The site will receive a pre-visit letter or e-mail two to three weeks prior to a proposed visit, confirming the dates of the visit and listing the items to be monitored during the visit. The monitoring team will typically consist of DCC staff cognizant with the relevant studies and data entry/management issues, and, if necessary, a clinical monitor

specifically hired by the DCC to perform such tasks. NICHD personnel may accompany the site monitoring team as well.

Site monitoring visits may be protocol-specific, site-specific (i.e., examining all studies and procedures at the site), or targeted (e.g., laboratory monitoring). The purpose of the visit will depend on the assignment, but may include:

- protocol-specific NRN study initiation assessment
- review of participant records and source document verification of trial data
- review of informed consent forms
- regulatory file review
- study close-out activity review

In addition, the monitors may assess the adequacy of the pharmacy, clinic, laboratory, institutional review board review process, and other facilities; medical records; case report forms; and any aspect of the clinical research that may affect participant safety. Special monitoring assignment visits may be requested of the DCC at the discretion of the NICHD, when necessary, to verify any particular aspects of trial conduct.

The site is requested to make arrangements for the monitors to meet with the appropriate study staff and institutional staff during the visit and to make every effort to ensure that all documentation to be monitored is readily accessible. The site is expected to identify an appropriate place for the monitors to work during the visit with, access to a telephone and a copy machine if possible.

The monitors will hold a summary meeting with site staff toward the end of the visit, typically on the last day, to review the findings of the visit. The monitors meet with the site Principal Investigator (PI) and any study staff that he or she would like to include. The monitors will leave a list of the pertinent findings with the PI at the end of the visit so that, corrective actions, if necessary, can begin at once. A written summary of the debriefing will be transmitted by fax or e-mail to the DCC Project Director within five days after the debriefing The Project Director may initiate follow-up discussions with the site and NICHD on the basis of this summary information.

1.2.2 Protocol Violations and Protocol Non-Adherence

The DCC is responsible for reporting protocol departures and violations found during site-monitoring visits. Protocol departures, deviations and violations are based on findings using the NICHD NRN Protocol and Manual of Procedures. The monitoring report includes protocol violations and protocol non-adherence events (departures or deviations). The term "protocol violation" is intended to be used for the more serious problems found.

The DCC will work jointly with the NICHD to assess the protocol event severity. For the purpose of this procedure, protocol events are defined as individual incidents or omissions in study conduct that result in:

1. Significant added risk to the participant, or
2. Non-adherence to significant protocol requirements, or

3. Significant non-adherence to required regulatory guidelines.

Examples of Protocol Events that will require formal documenting are following:

- enrollment of an ineligible participant
- informed consent not obtained prior to performing protocol-specified procedures
- non-compliance with study randomization and blinding procedures
- protocol-specified procedures not followed:

  Study subject non-compliance with the study protocol, including study treatment specifications, is not considered a reportable protocol event, but should be discussed by the Protocol Team.
- breach of participant confidentiality

Other concerns not listed above

1.3 Monitoring Reports

A detailed written report, based on the monitor's observations during the site monitoring visit, is completed by the monitor and reviewed by the DCC Project Director. The report will be distributed within 20 working days of the visit to the study PI, clinic/study coordinator and Pharmacist of Record (when applicable). The DCC Project Director will share this report with the NICHD.

1.3.1 Procedures for Site Response to Monitoring Reports

Upon receipt of the monitoring report, the site PI will review the report and identify issues noted in the report. If corrective actions are required, the PI should send notification to the DCC and NICHD outlining:

- how the site resolved or corrected the issue or a plan for resolution
- steps taken to prevent recurrence of issues
- disagreements with or errors, if any, in the DCC monitoring report findings and the reasons for the disagreement

A response from the site PI or designated site staff member is normally expected within 10 working days, although DCC and NICHD staff may request more rapid responses on potentially urgent issues.

The DCC Project Director reviews the response in conjunction with NICHD and:

- if the issues were satisfactorily resolved, note the resolution and send notification to the site that no further action needs to be taken
- if any issues remain unresolved, the DCC may request that the NRN PI or NICHD Program Scientist assist the site with problem resolution; the site must send a follow-up response to the DCC Project Director and NICHD after the problem has been resolved
- if major or multiple issues were noted, the DCC will discuss the possibility of more drastic remedial measures with the NICHD.

A final decision on recommended actions in the case of major or multiple issues is made by the Director of NICHD, in consultation with the NICHD Program Scientist, who will send a letter to inform the site PI and DCC Leadership of the decision.

1.3.2 Final Monitoring Report

A final monitoring report detailing findings and final resolutions (where applicable) will be sent to the site PI and the NICHD Program Scientist. A copy of the report will be kept on file at the DCC.

SITE MONITORING TRIP REPORT

Trial Name: _____

_____

Protocol ID: _____

Site Number: _____

Site Name: _____

Investigator Name: _____

Prior Monitoring Visits: _____

_____

Date(s) of This Visit: _____

Monitor Name:
Other Non-Site Personnel in Attendance:
Site Personnel in Attendance:

A. General Study Conduct (Provide comments underneath for all items marked "No")

1. The Investigator is adhering to the protocol and amendments ☐ Yes ☐ No

2. All Serious Adverse Events (SAEs) have been reported by site study staff ☐ Yes ☐ No

3. Informed consent properly obtained for each subject reviewed ☐ Yes ☐ No

4. Study facilities remain adequate ☐ Yes ☐ No

5. Study personnel and role of study staff remain unchanged ☐ Yes ☐ No

6. Clinical supplies are adequate (oximetry supplies, case report forms, other) ☐ Yes ☐ No

B. Data Collection

1. Case Report Forms (CRFs) reviewed against source documentation ☐ Yes ☐ No

2. Source documentation adequate to support entries on CRFs ☐ Yes ☐ No

Enrollment			CRF Status		
Subject Number	Date Enrolled	Time Enrolled	CRF In-house	Monitored	Follow-up In-house
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
Totals					

C. Investigational Product & Delivery Device

1. Was a study oximeter inventory performed ☐ Yes ☐ No

2. Are the storage conditions for the supplies and equipment adequate ☐ Yes ☐ No

3. Are all oximeters accounted for? (shipped vs. stored) ☐ Yes ☐ No

4. Are oximeters blinded ? ☐ Yes ☐ No

Oximeter Inventory				
Subject Number	Serial # CRF	Serial # Subject	Frequency of downloads.	# of Downloads Missed
Totals				

5. # of Subjects with documented use of Histogram / # of Subjects Reviewed. _____ /_____

D. In-House Subject Review

1. On study oximeter within 2 hours. ☐ Yes ☐ No

2. Study oximeter working properly, matches documented Serial # ☐ Yes ☐ No

3. Review ventilation data to determine if protocol being followed ☐ Yes ☐ No

4. Review histograms. ☐ Yes ☐ No

5. Deviations Noted ☐ Yes ☐ No

E. Essential Documents and IRB requirements

1. GDB approval current ☐ Yes ☐ No
   Expires (date):

2. SUPPORT approval current ☐ Yes ☐ No
   Expires (date):

3. Blood Gas laboratory certification current ☐ Yes ☐ No
   Lab Name:
   CAP (exp): CLIA (exp) Other (exp):

4. Amendments have been signed, submitted to the IRB and approved ☐ Yes ☐ No

5. SAEs reported to the IRB ☐ Yes ☐ No

F. Cumulative SAE List

Subject #	SAEs (Y or N)	# Reported (to RTI)	# Reconciled
1			
2			
3			
5			
6			
7			
8			
9			
10			

G. Cumulative Protocol Deviations and Violations List

Subject #	Deviations Found	Documented?	Reported
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

H. Explain resolutions to all outstanding issues from previous trip reports or other site contacts

I. List issues that require follow-up

J. Additional Comments

Completed By: _____ _____
Monitor Signature Date

Approved By: _____ _____
RTI Signature Date

From: Kathy J Auten
To: Zaterka-Baxter, Kristin
Cc: Conra Backstrom; Ellen Hale; Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins
Subject: Re: Support Oximeters
Date: Tuesday, November 07, 2006 9:22:44 AM

I am well-supplied with monitors.

Kathy J. Auten, MSHS
NICHD Neonatal Research Network Coordinator
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

"Zaterka-Baxter, Kristin" <kzaterka@rti.org> wrote on 11/06/2006 05:48:30 PM:

> Hi Ellen and all;
> Ellen, welcome back! If feasible, please send Monica Collins back
> the 3 blue oximeters Kathy Auten sent you mid October from Duke;
> they are UAB originals (listed below). The three orange were
> originally from Miami; please now send these to Connie at NM (address below).
>
> Connie, when you receive these 3 oranges from Emory; please send
> Monica Collins back their original 5 oranges with 2 blue originals
> (also listed below)
>
> Monica, when you receive the 3 blue oximeters back from Emory and 2
> blues back from NM that were originally your, if you can, please
> send the 4 blue oximeters with incorrect histograms to Masimo to get
> fixed. Once they are fixed, they should be sent to NM with the 1
> remaining orange from Miami (listed below).
>
> Connie, once you receive these 4 blue oximeters and the 1 remaining
> orange oximeter from UAB, you should have the 4 blues and 4 oranges
> that were originally from Miami. Please now return the remaining 3
> blue oximeters originally from UAB (listed below). Please send
> docking stations as well; I realize I do not have the correct
> docking station numbers per an email sent by Shirley Cosby 10/02/06.
>
> Kathy, please let me know if you are ok with the number of oximeters
> you have currently?
>
> This way everyone should have the oximeters that belong to them and
> we can keep track. Please double check all serial numbers at your
> site. These numbers are from my master list and hopefully are
> correct. Please all, check the shipping addresses below as well. THANKS!
>
> BLUE FROM EMORY TO GO TO UAB:
> 312119 docking station 062524
> 312272 docking station 061833
> 312225 docking station 061797
>
> ORANGE FROM EMORY TO GO TO NEW MEXICO:
> 317227 docking station 059866
> 317560 docking station 062543
> 317384 docking station 063202

> ORANGE FROM NEW MEXICO TO GO BACK TO UAB:
> 329709 docking station 74732

> 329689 docking station 74768

> 329713 docking station 73615

> 329703 docking station 79445

> 329706 docking station 74743

> 329083 BLUE docking station 77619

> 328935 BLUE docking station 75185

>
> BLUE FROM UAB TO MASIMO FOR HISTOGRAM FIX (these plus the 1 ORANGE
> 317438 should be sent to NM after the blues are returned with fixed

> histograms)

> 317219 BLUE

> 317363 BLUE

> 317420 BLUE

> 317431 BLUE

>

> BLUE FROM NM BACK TO UAB:

> 329207 BLUE

> 328981 BLUE

> 328981 BLUE

>

>

> SHIIPING ADDRESSES:

> University of New Mexico
> Department of Pediatrics
> 915 Camino de Salud NE

> Albuquerque NM 87131

> Attn: Connie Backstrom

>
> University of Alabama at Birmingham

> Division of Neonatology
> 525 New Hillman Building, UAB Station

> Birmingham AL 35294

> Attn: Monica Collins

>

> Please let me know if you have any questions or better suggestions.

>

> Thanks again!

> Kris

>

> Kris Zaterka-Baxter, RN, CCRP

> RTI International

> 4426 South Miami Blvd.

> Durham, NC 27703

> Telephone: (919) 485-7750

> Fax: (919) 485-7762

> kzaterka@rti.org
>
> From: Ellen Hale [mailto:Ellen.Hale@oz.ped.emory.edu]
> Sent: Monday, November 06, 2006 4:12 PM
> To: higginsr@mail.nih.gov; Zaterka-Baxter, Kristin

> Subject: Candida IRB renewal approval

>
> Please find attached our IRB renewal for Candida.
>
> Also, we have extra masimo monitors now if anyone needs them. I
> will keep them untill you tell me where to send them.
> Ellen

From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Missing ROP for Support
Date: Thursday, November 02, 2006 12:03:20 PM

I can't get a time for everyone. This was the best with just missing Kris.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 02, 2006 7:12 AM
To: Webb, Robin E.
Subject: Re: Missing ROP for Support

Is it possible to get everyone or not? If not, this will be ok

Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Webb, Robin E. <rwebb@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 01 16:34:05 2006
Subject: RE: Missing ROP for Support

Rose,

I have a time that everyone can make but Kris. Is that ok?

Thanks,

Robin

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 26, 2006 12:09 PM
To: Webb, Robin E.
Subject: FW: Missing ROP for Support

Robin

Can you set up a call with Jenny, Abhik, Kris, Neil Finer, Dale Phelps and myself to discuss ROP outcomes?
Thanks

Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, October 26, 2006 12:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Missing ROP for Support

Sounds like we may need a call to sort this one out.

Thanks

Abhik

From: Auman, Jeanette O.
Sent: Thursday, October 26, 2006 11:04 AM
To: 'Phelps, Dale'
Cc: Zaterka-Baxter, Kristin; nfiner@ucsd.edu; Das, Abhik
Subject: RE: Missing ROP for Support

We are currently getting the date of death from the NG03/NG05/NF10. The problem is there's no grace period between the date of last ROP exam (that doesn't show final status) until the date of death. Do we ask the coordinators for exams between the last exam reported and the date of death? If so, what time period between the last exam and the date of death do we continue asking for the final outcome? So, let say a patient died on 10/25/2006, but the last ROP exam was 08/26/2006 and did not show final ROP outcome, do we still ask for more exams after this last one? How many months/days between the last exam reported and death can we safely assume there will be no more exams and therefore no final outcome?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 26, 2006 10:51 AM
To: Auman, Jeanette O.
Cc: Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: RE: Missing ROP for Support

Hi Jeanie,

I think we need to discuss this with Kris and/or Dr. Das too.

Ironically, we have this situation covered nicely in the GDB.

Status = died

ROP outcome "undetermined"

We just need to be able to get the same conclusion from the ROP status form for SUPPORT

We need to have the coordinators be able to code "final outcome" as "died before further examinations"

Without changing the form: could we....

Enter the date of death on the next line (as an 'exam') and code the Location as "9" = Expired

When this code is used, all further items in the line would be left blank.

You would then know that there would be no further information to be obatined.

Would this work?

Alternatively, you could pick up the date of death (and ROP status) from the NGO3, but I'm not sure what to tell it next.

Dale

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Thursday, October 26, 2006 10:39 AM
To: Phelps, Dale

Subject: RE: Missing ROP for Support

Ok, that's sounds fine. I'll send you all the info about Lost to Follow-up cases, so you can see them. Actually, I have two.

Also, something else that came up that I should probably mention. At Duke, there is a patient who died one day after his/her last ROP exam and the software is currently asking for the final outcome. Obviously, there won't be another exam. This is alright for me to code, correct?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 25, 2006 11:11 PM
To: Auman, Jeanette O.
Subject: RE: Missing ROP for Support

I guess I would just like to review the circumstances of each case.

By doing this now, the coordinators have to justify. They learn we are serious that we want an outcome. I know they know that, but I want them to KNOW that.

:-)

Dale

Dale L. Phelps, MD

Pediatrics and Ophthalmology

Pediatrics, Box 651

601 Elmwood Ave.

Rochester, NY 14642

585.275.2972

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Wed 10/25/2006 9:07 PM
To: Phelps, Dale
Subject: RE: Missing ROP for Support

What I should have said was if the NF12 was completed stating that no information was obtained for the patient, Q. A2 "Is information available for this child from indirect sources?" = 'N' and the Q. 2a. Date of last contact is a date prior or the same as the last SUPP10, then could we assume?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 25, 2006 8:59 PM
To: Auman, Jeanette O.
Subject: Re: Missing ROP for Support

It is quite possible to have a final ROP outcome after discharge home and long before the 18 month visit. Sometimes all it takes to learn that is a phone contact, of office records from the ophthalmologist.
So I don't think the "lost to follow up" form is suffucuent.
Dale
Dale Phelps
(585)275-2972
University of Rochester

-----Original Message-----
From: Auman, Jeanette O. <joa@rti.org>
To: Phelps, Dale
CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Wed Oct 25 20:54:06 2006
Subject: RE: Missing ROP for Support

I'm sorry if I didn't include you in on the email to Dr. Finer and Dr. Higgins. I haven't received any responses as of yet from them.

The Lost to follow-up code would be obtained from the 18 - 22 month follow-up data. So, if an NF12 form was keyed, the site is saying that they can not get the patient back in for a visit. I thought it would be practical to infer from this that they would never get a final ROP outcome if this occurred. If you still want to be the one who oks us coding that patient as being acceptable to not have a ROP status, that's fine. Just thought I might save you some time and aggrevation!

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 25, 2006 8:40 PM

To: Auman, Jeanette O.
Cc: Zaterka-Baxter, Kristin
Subject: RE: Missing ROP for Support

Whoops, I forgot to say that I would be happy to be part of that discussion !!!!

In STOP-ROP we used an ophthalmics endpoint committee to evaluate cases where not all exams were done. This was occasionally helpful.

We can usually infer some information from the 18-22 follow up as well.

There's stuff to discuss

Dale

Dale L. Phelps, MD

Pediatrics and Ophthalmology

Pediatrics, Box 651

601 Elmwood Ave.

Rochester, NY 14642

585.275.2972

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Tue 10/24/2006 10:13 AM
To: Phelps, Dale
Cc: Zaterka-Baxter, Kristin
Subject: RE: Missing ROP for Support

Ok, I will.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 24, 2006 10:13 AM
To: Auman, Jeanette O.
Subject: Re: Missing ROP for Support

Hi Jeannie,
This is a primary outcome. It has to be dealt with.
Dr. Finer, Dr. Higgins and-or the Subcommittee should discuss. There are options. Can you please foreward to Dr. Finer, Dr. Das, and Dr. Higgins? (I am on Blackberry.)
Dale

Dale Phelps
(585)275-2972
University of Rochester

-----Original Message-----
From: Auman, Jeanette O. <joa@rti.org>
To: Phelps, Dale
CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tue Oct 24 09:49:36 2006
Subject: Missing ROP for Support

Hi Dale,

We're discovering that there are a few patients who are lost to follow-up and the final ROP diagnosis will never be obtained. Initially when you and Scott discussed the missing ROP report, I believe you and he decided that you would officially ok all of these cases before we coded the software to no longer request these missing exams. Do you still want to do this on a case by case basis or should I code the report to no longer expect the final exam if the patient has been coded as lost to follow-up on the NF12?

Thanks,

Jenny

Jeanette Auman

Programmer/Analyst III

(919) 220-9023

joa@rti.org

From:	Wade Rich
To:	Neil Finer; Zaterka-Baxter, Kristin
Cc:	Das, Abhik; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Pickett, James; Gantz, Marie
Subject:	RE: FW: SUPPORT FU
Date:	Thursday, November 02, 2006 10:29:34 AM

As this decreases work for RTI at the other end, and is fairly simple at this end for Kris, I think it is both reasonable to do for this trial and something to keep in mind for future forms as well.
Wade

-----Original Message-----
From: Neil Finer
Sent: Wednesday, November 01, 2006 9:33 PM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Auman, Jeanette O.; Pickett, James; Gantz, Marie
Subject: RE: FW: SUPPORT FU

This may be a reasonable revision
Neil

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, November 01, 2006 7:32 AM
To: Neil Finer
Cc: Das, Abhik; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Auman, Jeanette O.; Pickett, James; Gantz, Marie
Subject: RE: FW: SUPPORT FU

Hi,
A status code for 'withdrawn from study' on the Supp09 can be added quite easily. We've had a few withdrawals and they have been documented on the protocol deviation form. We realize it's not a study deviation but is currently the only place to document the event. If a withdrawal code seems reasonable to add for study status, I can include it in the current revisions.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Tuesday, October 31, 2006 6:54 PM
To: kurt.schibler@cchmc.org; Roger Faix; wcarlo@peds.uab.edu; mcw3@po.cwru.edu; Das, Abhik; Petrie, Carolyn; Poole, W. Kenneth; srhintz@stanford.edu; nfiner@ucsd.edu; Michele.Walsh@UHhospitals.org; Timothy_Stevens@URMC.Rochester.edu; alaptook@wihri.org

Subject: Re: FW: SUPPORT FU

Don't we need a code for SUPP09 that allows us to note an A. INFANT OUTCOME as "withdrew from study"?

Brad

>>> "Neil Finer" <nfiner@ucsd.edu> 10/13/2006 4:04:48 PM >>>
FYI

-----Original Message-----
From: Neil Finer
Sent: Friday, October 13, 2006 12:53 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPPORT FU

Hi Rose.
I am concerned about the time required to do the Bayley III. If the follow-up PIs are unanimous about accepting this exam, I would support this position Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Friday, October 13, 2006 7:54 AM
To: Michele.Walsh@UHhospitals.org; Neil Finer; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: Re: SUPPORT FU

Please note - we are NOT to include gross and fine motor elements as these are duplicative in the neuro exam.
The Bayley III will take less than one hour in this fashion.
More discussion is welcome!
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Walsh, Michele <Michele.Walsh@UHhospitals.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; alaptook@wihri.org <alaptook@wihri.org>; adas@rti.org <adas@rti.org>; poo@rti.org <poo@rti.org>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; bradley.yoder@hsc.utah.edu <bradley.yoder@hsc.utah.edu>
Cc: Timothy_Stevens@URMC.Rochester.edu <Timothy_Stevens@URMC.Rochester.edu>; srhintz@stanford.edu <srhintz@stanford.edu>; petrie@rti.org <petrie@rti.org>
Sent: Fri Oct 13 11:48:24 2006
Subject: RE: SUPPORT FU

After listening to the concerns of the Gold Standard examiners about the considerable longer length of time for the Bayley III and the estimate that only 75% will get a score: I am gravely concerned about changing to the Bayley III. Since the intent of the trial is to compare two treatments, I think it is less important to understand what domain the deficits are in: something that I understand is of vital interest to those doing neonatal fu like the 'generic FU program'. I think our primary goal in this trial is to compare the treatments and ensure that those in one sat range vs the other are not harmed. I understand that it is difficult to

have two evaluations going on at the same time- but for SUPPORT I do NOT agree with changing to the Bayley III. WE can switch when SUPPORT is completed: yet another reason to finish SUPPORT expeditiously- perhaps by increasing the number of enrolling centers.
Michele

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Friday, October 13, 2006 9:52 AM
To: nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: SUPPORT FU

Hi,
The follow up PI's have discussed the pros and cons of Bayley II and III exams for SUPPORT FU. They have voted unanimously to perform the Bayley III to include cognitive, receptive and expressive language elements and NOT to include gross and fine motor elements as these are duplicative in the neuro exam. There was also a vote to consider changing the timing of the window - 18-22 months (11 votes) to 24-28 months (4 votes) as the Bayley III is a little easier as children get a little older.

Bayley III certifications videos are due by October 31. If we do not have the videos by Thanksgiving from the 15 sites whose windows will open in late 2006 or early 2007, this will need to come back to the group for reconsideration (I will send out weekly reminders in November to sites with missing videos).

The FU PI's are committed to instituting the Bayley III at the sites despite the concerns from the Gold Standard examiners raised over the last two days.

Let me know if the subcommittee is ok with this by Monday, October 16.
Thanks for your patience and valuable contribution to the discussion!
Rose

Sent from my BlackBerry Wireless Handheld

From: Duara, Shahnaz
To: Zaterka-Baxter, Kristin; Navarrete, Cristina; sduara@miami.edu; Everett, Ruth
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.
Subject: RE: SUPPORT GROWTH SECONDARY STUDY
Date: Tuesday, October 31, 2006 5:02:22 PM

That sounds fine. Thanks for everything.
Shahnaz

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, October 31, 2006 4:40 PM
To: Navarrete, Cristina; sduara@miami.edu; Everett, Ruth
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.
Subject: FW: SUPPORT GROWTH SECONDARY STUDY

Hi,
We will ask the Center to enroll these infants in support however there is not a protocol deviation form for this study. We should ask this center to document an asterisk for any required data field where the measurement was not obtained by the length board, then F5 to allow a comment and record the length of the measurements taken by tape measure and the reason why it was not by length board per protocol. This way, the statistician would never combine the two types of measurements in analysis. Please let me know if this sounds feasible or if anyone has any questions or concerns.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 31, 2006 3:14 PM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT GROWTH SECONDARY STUDY

From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Thursday, October 26, 2006 1:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT GROWTH SECONDARY STUDY

Hi Rose and Kris, I spoke with Dr. Duara concerning this matter and we agree that the centers should continue the measurements and just make a comment or complete a protocol violation to why a measurement was not obtained because there may be other reasons as well that may prevent the staff from using the length board such as when the babies are on the oscillator or his/her condition is too unstable for handling which is quite common in the smaller babies during sepsis and complications from the PDA. So I think these missing data points should be very similar in all instances and recorded as such. Also, Cristina contact information is 305 585-6408 office to the division of neonatology 305 750-(b) (6) pager number and she has an office in the Batchelor building 305 243-6457.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 26, 2006 9:46 AM
To: Navarrete, Cristina; Duara, Shahnaz; Everett, Ruth
Cc: Zaterka-Baxter, Kristin
Subject: SUPPORT GROWTH SECONDARY STUDY

HI,
For the Support growth study, if the length cannot be measured during the first week of life due to nursing practice, should those sites NOT participate in the study?
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: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Masimo Pulse Oximeter
Date: Tuesday, October 31, 2006 1:11:41 PM

Rose,
We don't have any more Moms consented for SUPPORT so we should be able to wait until tomorrow. Just as long as we don't have another rush like this morning.
Thanks,
Nancy

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 10/31/2006 11:35 AM >>>
Nancy
I just spoke to Georgia McDavid in Houston and she will send you two blue ones - let me know if that will suffice and do you think you will need them before the morning FEDEX delivery tomorrow?
Thanks
rose

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Tuesday, October 31, 2006 12:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Masimo Pulse Oximeter

Rose,
We need two blue pulse oximeters. We just admitted twins and have no blue ones left.
Thanks,
Nancy

Nancy A. Miller, R.N.
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-502
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From: Michelle Tidwell
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ellen Hale; Susie Buchter; kzaterka@rti.org; Anthony Piazza; Barbara Stoll
Subject: SUPPORT
Date: Monday, October 30, 2006 9:22:27 AM

Hi Everyone,

Baby # (b) (6) was enrolled in SUPPORT on (b) (6) morning at 00:59. This baby died (b) (6) (b) (6). Cause of death was not related to the study.

Michelle
Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899(b) (6) pager

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: FW: Missing ROP for Support
Date: Thursday, October 26, 2006 12:30:06 PM

True. Since the primary outcome is death or ROP, for the primary analysis it doesnt matter whether we have a definitive ROP diagnosis if death has occurred by status. One question I am not sure about (need to see the protocol) is what hapens if death occurs after release from hospital -- does death at any point in time qualify as the primary outcome?

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 26, 2006 12:26 PM
To: Das, Abhik
Subject: RE: Missing ROP for Support

That is appropriate (death is an outcome).

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, October 26, 2006 12:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Missing ROP for Support

FYI

From: Auman, Jeanette O.
Sent: Thursday, October 26, 2006 12:16 PM
To: nfiner@ucsd.edu
Cc: Das, Abhik; Zaterka-Baxter, Kristin; 'Phelps, Dale'
Subject: FW: Missing ROP for Support

Do you feel it's appropriate if the interval between the last ROP exam and death is less than 1 week that we no longer request further eye exam data for that patient from the center?

Thanks,
Jenny

Jeanette Auman
Programmer/Analyst III
(919) 220-9023
joa@rti.org

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 26, 2006 12:04 PM
To: Auman, Jeanette O.

Subject: RE: Missing ROP for Support

It depends on what the eye exam shows (unfortunately).

If the ROP is in the extremely active phase, there should be no more than one week between exams.
If it is in zone II, no more than two weeks, (unless it is very active) or unless it is regressing in which case it could be longer, or...
Etc.

I think it will be easier to look at each "situation' than to program the algorithm! :-(

OK: You can, at least, use this:
"If the interval between the last ROP exam and death is less than 1 week, do not request further eye exam data from the center."
Please see if Dr. Finer is ok with this.

Dale

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Thursday, October 26, 2006 11:04 AM
To: Phelps, Dale
Cc: Zaterka-Baxter, Kristin; nfiner@ucsd.edu; Das, Abhik
Subject: RE: Missing ROP for Support

We are currently getting the date of death from the NG03/NG05/NF10. The problem is there's no grace period between the date of last ROP exam (that doesn't show final status) until the date of death. Do we ask the coordinators for exams between the last exam reported and the date of death? If so, what time period between the last exam and the date of death do we continue asking for the final outcome? So, let say a patient died on 10/25/2006, but the last ROP exam was 08/26/2006 and did not show final ROP outcome, do we still ask for more exams after this last one? How many months/days between the last exam reported and death can we safely assume there will be no more exams and therefore no final outcome?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 26, 2006 10:51 AM
To: Auman, Jeanette O.
Cc: Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: RE: Missing ROP for Support

Hi Jeanie,
I think we need to discuss this with Kris and/or Dr. Das too.

Ironically, we have this situation covered nicely in the GDB.
Status = died
ROP outcome "undetermined"

We just need to be able to get the same conclusion from the ROP status form for SUPPORT

We need to have the coordinators be able to code "final outcome" as "died before further examinations"

Without changing the form: could we....
Enter the date of death on the next line (as an 'exam') and code the Location as "9" = Expired

When this code is used, all further items in the line would be left blank.
You would then know that there would be no further information to be obatined.

Would this work?

Alternatively, you could pick up the date of death (and ROP status) from the NGO3, but I'm not sure what to tell it next.

Dale

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Thursday, October 26, 2006 10:39 AM
To: Phelps, Dale
Subject: RE: Missing ROP for Support

Ok, that's sounds fine. I'll send you all the info about Lost to Follow-up cases, so you can see them. Actually, I have two.

Also, something else that came up that I should probably mention. At Duke, there is a patient who died one day after his/her last ROP exam and the software is currently asking for the final outcome. Obviously, there won't be another exam. This is alright for me to code, correct?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 25, 2006 11:11 PM
To: Auman, Jeanette O.
Subject: RE: Missing ROP for Support

I guess I would just like to review the circumstances of each case.
By doing this now, the coordinators have to justify. They learn we are serious that we want an outcome. I know they know that, but I want them to KNOW that.
:-)

Dale

Dale L. Phelps, MD
Pediatrics and Ophthalmology
Pediatrics, Box 651
601 Elmwood Ave.
Rochester, NY 14642

585.275.2972

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Wed 10/25/2006 9:07 PM
To: Phelps, Dale
Subject: RE: Missing ROP for Support

What I should have said was if the NF12 was completed stating that no information was obtained for the patient, Q. A2 "Is information available for this child from indirect sources?" = 'N' and the Q. 2a. Date of last contact is a date prior or the same as the last SUPP10, then could we assume?

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]

Sent: Wednesday, October 25, 2006 8:59 PM
To: Auman, Jeanette O.
Subject: Re: Missing ROP for Support

It is quite possible to have a final ROP outcome after discharge home and long before the 18 month visit. Sometimes all it takes to learn that is a phone contact, of office records from the ophthalmologist. So I don't think the "lost to follow up" form is suffucuent.
Dale
Dale Phelps
(585)275-2972
University of Rochester

-----Original Message-----
From: Auman, Jeanette O. <joa@rti.org>
To: Phelps, Dale
CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Wed Oct 25 20:54:06 2006
Subject: RE: Missing ROP for Support

I'm sorry if I didn't include you in on the email to Dr. Finer and Dr. Higgins. I haven't received any responses as of yet from them.

The Lost to follow-up code would be obtained from the 18 – 22 month follow-up data. So, if an NF12 form was keyed, the site is saying that they can not get the patient back in for a visit. I thought it would be practical to infer from this that they would never get a final ROP outcome if this occurred. If you still want to be the one who oks us coding that patient as being acceptable to not have a ROP status, that's fine. Just thought I might save you some time and aggrevation!

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 25, 2006 8:40 PM
To: Auman, Jeanette O.
Cc: Zaterka-Baxter, Kristin
Subject: RE: Missing ROP for Support

Whoops, I forgot to say that I would be happy to be part of that discussion !!!!

In STOP-ROP we used an ophthalmics endpoint committee to evaluate cases where not all exams were done. This was occasionally helpful.

We can usually infer some information from the 18-22 follow up as well.

There's stuff to discuss

Dale

Dale L. Phelps, MD

Pediatrics and Ophthalmology

Pediatrics, Box 651

601 Elmwood Ave.

Rochester, NY 14642

585.275.2972

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Tue 10/24/2006 10:13 AM
To: Phelps, Dale
Cc: Zaterka-Baxter, Kristin
Subject: RE: Missing ROP for Support

Ok, I will.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 24, 2006 10:13 AM
To: Auman, Jeanette O.
Subject: Re: Missing ROP for Support

Hi Jeannie,
This is a primary outcome. It has to be dealt with.
Dr. Finer, Dr. Higgins and-or the Subcommittee should discuss. There are options. Can you please foreward to Dr. Finer, Dr. Das, and Dr. Higgins? (I am on Blackberry.)
Dale

Dale Phelps
(585)275-2972
University of Rochester

-----Original Message-----
From: Auman, Jeanette O. <joa@rti.org>
To: Phelps, Dale

CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tue Oct 24 09:49:36 2006
Subject: Missing ROP for Support

Hi Dale,

We're discovering that there are a few patients who are lost to follow-up and the final ROP diagnosis will never be obtained. Initially when you and Scott discussed the missing ROP report, I believe you and he decided that you would officially ok all of these cases before we coded the software to no longer request these missing exams. Do you still want to do this on a case by case basis or should I code the report to no longer expect the final exam if the patient has been coded as lost to follow-up on the NF12?

Thanks,

Jenny

Jeanette Auman

Programmer/Analyst III

(919) 220-9023

joa@rti.org

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]; Navarrete, Cristina; Everett, Ruth
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT GROWTH SECONDARY STUDY
Date: Thursday, October 26, 2006 11:05:54 AM

Rose,

We could go either way – either accept missing data points, or exclude the center, but we would prefer to make that unnecessary. Can you give us a sense of how many centers would be affected? I know that Tina had a query from Tufts regarding use of an alternate method to the length board for the early measurements – that would really mess us up methodologically and we agreed to make alternative ways of making measurements a no-no. If a center is willing to be dinged for missing data points, we could have the original birth length and then pick up length measures with the board from week 2 onwards.

Hope enrollment in SUPPORT picks up!
Shahnaz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 26, 2006 10:46 AM
To: Navarrete, Cristina; Duara, Shahnaz; Everett, Ruth
Cc: Zaterka-Baxter, Kristin
Subject: SUPPORT GROWTH SECONDARY STUDY

HI,
For the Support growth study, if the length cannot be measured during the first week of life due to nursing practice, should those sites NOT participate in the study?
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: CATHY A. GRISBY
To: Higgins, Rosemary (NIH/NICHD) [E]; Kurt Schibler
Cc: Gantz, Marie; Das, Abhik
Subject: RE: Missing ROP INFO
Date: Wednesday, October 25, 2006 11:22:11 AM

Hi,

That sounds reasonable. I've forwarded this on to Tari and Stacey who do our F/U and will let you know.

Cathy

---- Original message ----

Date: Mon, 23 Oct 2006 11:50:57 -0400
From: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
Subject: RE: Missing ROP INFO
To: "CATHY A. GRISBY" <grisbyca@email.uc.edu>, "Kurt Schibler" <kurt.schibler@cchmc.org>
Cc: "Gantz, Marie" <mgantz@rti.org>, "Das, Abhik" <adas@rti.org>

If we have permission for follow up for
these children, can we ask the parents if we can obtain the information from
site B?

Thanks

Rose

From: CATHY A. GRISBY
[mailto:grisbyca@email.uc.edu]

Sent: Monday, October 23, 2006
11:48 AM

To: Higgins, Rosemary (NIH/NICHD)
[E]; Kurt Schibler

Cc: Gantz, Marie; Das, Abhik

Subject: Re: Missing ROP INFO

Hi,

We have
been addressing these edits since May and have had contact with RTI during this time period. An NF10 has been entered for all these babies. There are '*' (permanently missing info) and comments (F5 and F9) that have been entered. Individually here are the situations for each of these babies.

(b) (6)
(b) (6) were transferred to site [redacted] where, at that time, we did not have IRB approval. No data could be collected for the SUPPORT trial once transfer occurred.

(b) (6)
(b) (6) have parents that did not bring their babies back for outpatient eye exams. The follow up coordinators have been in/attempted contact multiple times with these parents.

(b) (6)
withdrew from the study within the first few days. All data collection was stopped.

Please
let us know if there are any further modifications we can do to the data to address these situations.

Thanks,

Cathy

---- Original message ----

Date:
Fri, 20 Oct 2006 12:32:25 -0400

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

Subject: Missing ROP INFO

To: "Kurt Schibler"
<kurt.schibler@cchmc.org>, <grisbyca@email.uc.edu>

Cc: "Gantz, Marie"
<mgantz@rti.org>, "Das, Abhik" <adas@rti.org>

```
#MiraWebMsgDiv

st1\:*{behavior:url(#default#ieooui) }
```

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

50 weeks PMA has been reached and final

ROP exam status has not been reported on the SUPP10 for either eye.

11 (b) (6)

HI,

We need a few ROP outcomes for SUPPORT – these are essential for the upcoming planned looked by the DSMC at 25% of the patients reaching status. Please submit them (or indicate loss if lost).

Thanks for all the effort!!!

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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301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Neil Finer
To: Das, Abhik; M. Bethany Ball; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT randomization
Date: Tuesday, October 24, 2006 7:30:50 PM

Hi Bethany
I agree with all of your actions
Be well
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, October 24, 2006 2:05 PM
To: M. Bethany Ball; higginsr@mail.nih.gov
Cc: Neil Finer
Subject: RE: SUPPORT randomization

I think a difference of 18 minutes should not matter, unless Rose/Neil think there are clinical reasons for believing otherwise. Thanks for letting us know.

Abhik

-----Original Message-----
From: M. Bethany Ball [mailto:mbball@stanford.edu]
Sent: Tuesday, October 24, 2006 5:04 PM
To: higginsr@mail.nih.gov; Das, Abhik
Subject: SUPPORT randomization

Dear Rose and Abhik,

We had some confusion over the week-end about a SUPPORT randomization. A family was consented for the study several weeks ago and on (b) (6) (b) (6) the decision was made to deliver. At that time the gestational age was 27 weeks 6 days. Randomization occurred on (b) (6) but the baby wasn't born until 0018 on (b) (6) by which time he was 28 weeks and out of the eligibility window. The delivery room intervention was followed but the baby was not put on the study pulse ox until I found out what had gone on, invoked the "intent to treat" paradigm, and set him up shortly before 12 hours of age. Since that time the protocol has been followed.

We're submitting a violation for the late application of the PO. Remediation to reduce the time between randomization and delivery is underway. Is there anything else you want us to do?

Thanks,
Beth
--
Bethany Ball
Neonatal and Developmental Medicine
Stanford University
750 Welch Road, Suite 315
Palo Alto, CA 94304

Tel (650) 725 8342
Fax (650) 725 8351

From: Das, Abhik
To: Walsh, Michele; Abbot Laptook; Neil Finer
Cc: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@po.cwru.edu; kurt.schibler@cchmc.org; WCarlo@PEDS.UAB.edu; Roger.Faix@hsc.utah.edu; wrich@ucsd.edu; Petrie, Carolyn
Subject: RE: Support forms
Date: Tuesday, October 24, 2006 1:38:47 PM

Sorry for the delayed response. It is actually pretty difficult to provide a precise estimate along the lines suggested by Michele. It depends very much on what the additional field in the form does to the collection of the data. If it is the addition of a gate question or something else that causes a change of the logic in the end for record check then it takes additional time to program and test. If it is just an additional field that may be optional to key, then it would take less effort.

When there is a change to a form, our programmers need to add it to the codebook, program it so that it will update the site's data tables, add it to the form and report and finally add it to the final record check. Then the Data Entry software is tested to make sure everything was added correctly, and if so, it is set up to be sent out via the transmission system. Once that is done, it is added to our master database, added to the SAS conversion codebook, and if batch edits have already been created, added to the batch edit code.

All this might take a programmer 3 to 4 hours to add a simple field to the software, about an hour to test (if there are no errors), and 30 minutes to an hour to add it to the processing. The time it takes would go up from there depending on the programmatic complexity of the addition. The number of subjects in a study does not matter much as far as the programming effort goes -- a form change/addition is one piece of code that can apply to 1 or 100 or 1000 subjects as appropriate. The thing that also should be factored into the cost estimate is whether and how much such changes make data collection easier for the coordinators and make for better data analysis.

Thanks

Abhik

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, October 16, 2006 4:20 PM
To: Abbot Laptook; Neil Finer
Cc: Zaterka-Baxter, Kristin; HigginsR@mail.nih.gov; mcw3@po.cwru.edu; kurt.schibler@cchmc.org; Das, Abhik; WCarlo@PEDS.UAB.edu; Roger.Faix@hsc.utah.edu; wrich@ucsd.edu; Petrie, Carolyn; Das, Abhik

Subject: RE: Support forms

Nancy and I also reviewed the forms. I agree to editing the supp04 with the clarifying statement

and making all of the other changes as suggested.

For the future- It would be helpful if Abhik gets us an idea of the cost of a single data item-

for instance if we knew that 1 data element costs: $100, (or whatever the right figure is:

for coordinator time, software programming, data entry) then it might give us pause to add

one data element for 1100 kids on 14 days: which is 15, 400 more data entries! By my estimate

the additions to the forms generate an additional 323,400 data entries.

Michele

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Friday, October 13, 2006 6:12 PM
To: Neil Finer
Cc: kzaterka@rti.org; HigginsR@mail.nih.gov; mcw3@po.cwru.edu; kurt.schibler@cchmc.org; adas@rti.org; WCarlo@PEDS.UAB.edu; Roger.Faix@hsc.utah.edu; wrich@ucsd.edu; petrie@rti.org

Subject: Support forms

Neil

The changes that were suggested to the forms look fine to me. With regard to supp04, I would go with the addition of the clarifying statement so that no DMS changes are needed. Although I do understand the concern of changing forms and the difficulty this may pose when you collate data, I think the overall benefits of the changes to the coordinators will enhance accurate data collection. AL

From: Auman, Jeanette O.
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; nfiner@ucsd.edu
Subject: FW: Missing ROP for Support
Date: Tuesday, October 24, 2006 12:21:18 PM

Please see below. Thank you.

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 24, 2006 10:13 AM
To: Auman, Jeanette O.
Subject: Re: Missing ROP for Support

Hi Jeannie,
This is a primary outcome. It has to be dealt with.
Dr. Finer, Dr. Higgins and-or the Subcommittee should discuss. There are options. Can you please foreward to Dr. Finer, Dr. Das, and Dr. Higgins? (I am on Blackberry.)
Dale

Dale Phelps
(585)275-2972
University of Rochester

-----Original Message-----
From: Auman, Jeanette O. <joa@rti.org>
To: Phelps, Dale
CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Tue Oct 24 09:49:36 2006
Subject: Missing ROP for Support

Hi Dale,

We're discovering that there are a few patients who are lost to follow-up and the final ROP diagnosis will never be obtained. Initially when you and Scott discussed the missing ROP report, I believe you and he decided that you would officially ok all of these cases before we coded the software to no longer request these missing exams. Do you still want to do this on a case by case basis or should I code the report to no longer expect the final exam if the patient has been coded as lost to follow-up on the NF12?

Thanks,

Jenny

Jeanette Auman

Programmer/Analyst III

(919) 220-9023

joa@rti.org

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Missing ROP INFO
Date: Tuesday, October 24, 2006 10:37:59 AM

Thanks, Rose. It is not a problem that the exam is after 50 weeks PMA. That is just the grace period we give the centers so that they do not receive a missing ROP status error before that time.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 24, 2006 10:00 AM
To: Gantz, Marie
Subject: Fw: Missing ROP INFO

FYI

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Monica Konstantino <monica.konstantino@yale.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Oct 24 09:40:48 2006
Subject: Re: Missing ROP INFO

Higgins, Rosemary (NIH/NICHD) [E] wrote:

If you have that exam, please submit it and let RTI know that it is out of the window.

Thanks
Rose

From: Monica Konstantino
[mailto:monica.konstantino@yale.edu]
Sent: Friday, October 20, 2006 4:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Missing ROP INFO

Higgins, Rosemary (NIH/NICHD) [E] wrote:

13

(b) (6)

50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,

We need a few ROP outcomes for SUPPORT - these are essential for the upcoming planned looked by the DSMC at 25% of the patients reaching status. Please submit them (or indicate loss if lost).

Thanks for all the effort!!!

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

(For overnight delivery, use Rockville , MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

Hi Rose,

In regard to this edit; the infant's exam on (b) (6) (which was close to 50 weeks PMA) was the last exam this infant had until this fall when the baby was 15 months of age (chronological age). At the time of the (b) (6) appt the ophalmologist had requested to see the baby in 3 weeks. The mother did not keep the appt and attempts to reach her failed. They did catch up with her and she was seen as mentioned above at 15 months of age (chronological age). Would you like the results of this exam. We did not know if it would just generate another edit since it would be out of the window of 50 weeks PMA. Please let me know and I would be happy to send this info along.

Thanks,

Monica

We did get the results of the eye exam done on (b) (6). That exam showed fully mature

exam with no ROP, zone 4, stage 0. We have have submitted the info on the SUPP10 form. Please let me know if you need any more info.

Monica

From: Michelle Tidwell
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ellen Hale; Barbara Stoll; Das, Abhik; Gantz, Marie
Subject: Re: Missing ROP INFO
Date: Friday, October 20, 2006 4:25:18 PM

Hi Dr. Higgins,

Thanks for the update on ROP outcomes for SUPPORT.

(b) (6) - I am still waiting on records.
(b) (6) now has a final outcome entered.
(b) (6) has moved to Texas and we are working with one of the centers there to find out his final outcome.

Thank you and have a wonderful weekend.

Michelle

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network
Emory University
(404) 616-5397 office (404) 899-(b) (6) pager

From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu
Cc: Gantz, Marie; Das, Abhik
Subject: RE: Missing ROP INFO
Date: Friday, October 20, 2006 2:17:52 PM

Rose,
I have just transmitted again this week.
Pt.(b) (6) died prior to any eye exams
Pt.(b) (6) had 2 exams (one report we just got yesterday) indicating maturity
Pt.(b) (6) is being scheduled for an examination by the pediatrician. This family did not return for their scheduled exam. The information before discharge showed one exam with no rop and vessels in zone 3.

Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 10/20/2006 11:35 AM
To: wacarlo@uab.edu; Monica Collins
Cc: Gantz, Marie; Das, Abhik
Subject: Missing ROP INFO

16	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,
We need a few ROP outcomes for SUPPORT – these are essential for the upcoming planned looked by the DSMC at 25% of the patients reaching status. Please submit them (or indicate loss if lost).

Thanks for all the effort!!!

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: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: MISSING ROP INFO
Date: Friday, October 20, 2006 1:12:46 PM

submitted Yesterday.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 20, 2006 9:40 AM
To: Neil Finer; Wade Rich
Cc: Gantz, Marie; Das, Abhik
Subject: MISSING ROP INFO

22 (b) (6) 50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

HI,
We need a few ROP outcomes for SUPPORT – these are essential for the upcoming planned looked by the DSMC at 25% of the patients reaching status. Please submit them (or indicate loss if lost).

Thanks for all the effort!!!

Rose

Rosemary D. Higgins, M.D.
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]; Michael O`Shea
Cc: Gantz, Marie; Das, Abhik
Subject: RE: MISSING ROP INFO
Date: Friday, October 20, 2006 12:55:37 PM

Will be able to obtain but will unable to complete the forms and submit until after the first week of November, if the office records are made available to me in the next two weeks. When is the upcoming planned look by the DSMC at this data?

Nancy

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 20, 2006 12:39 PM
To: Michael O`Shea; Nancy Peters
Cc: Gantz, Marie; Das, Abhik
Subject: MISSING ROP INFO

HI,
We need a few ROP outcomes for SUPPORT – these are essential for the upcoming planned looked by the DSMC at 25% of the patients reaching status. Please submit them (or indicate loss if lost).

Thanks for all the effort!!!

Rose

20	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Neil Finer
To: Walsh, Michele; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; Wade Rich; Petrie, Carolyn
Cc: Stevens, Timothy
Subject: RE: Breathing Outcomes Report
Date: Thursday, October 19, 2006 12:26:33 PM

Hi Everyone
Here is a report from Tim regarding the Breathing Outcomes.

The Breathing Outcomes Study is coming along nicely. As of September 30, 2006, there were 302 eligible patients, 153 have consented, 149 have completed the baseline interview, 104 have completed the 6 month interview and 32 have completed the 12 month interview. No one has reached the 18 month window.

I am pleased that the number of patients giving consent for Breathing Outcomes is increasing faster than the number of eligible patients, suggesting that families who were enrolled in SUPPORT before Breathing Outcomes began are being approached and are giving consent for Breathing Outcomes (since 7/31/06, 25 new patients became eligible for Breathing Outcomes and 32 patients gave consent!).

Please let Tim know if you have any concerns
Thanks
Neil

From: Wade Rich
To: kwatterberg@salud.unm.edu; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Cc: jrohr@salud.unm.edu; msayre@masimo.com
Subject: FW: masimo sensors
Date: Thursday, October 19, 2006 10:09:37 AM
Attachments: SofTouch NeoPT-L.pdf
LNOP Neo-L.pdf

Kristi,

You should have a local rep who can help you order them. I am cc'ing this email to our Masimo contact for the trial, Maribeth Sayre, who is their medical officer. There are two probes which we find work best for our populations:

The soft touch sensors work best for the very smallest babies with sensitive skin. The LNOP sensor is a little more durable and works for babies if they keep their sensor on for longer periods of time, or are in the bigger strata. (These are my opinions, and do not necessarily represent the opinions of Masimo, the NICHD, or any rational person.)

These sensors are not specific to the study like the oximeters, so you can buy them from your representative or the main site, whichever is easier for you. I do not actually know if you can order directly on line, or if they will direct you to a local representative.

Hope this helps. Let me know if you have further questions.

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-(b) (6)

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 19, 2006 6:40 AM
To: Neil Finer; Wade Rich
Subject: Fw: masimo sensors

Wade or Neil - can you send NewMexico the ordering info for the oximeter sensors?

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Kristi Watterberg <KWatterberg@salud.unm.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Julie Rohr <JRohr@salud.unm.edu>
Sent: Thu Oct 19 09:37:46 2006
Subject: Re: masimo sensors

That might be helpful - otherwise we'll order off their website. Thanks, Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>>> 10/19/2006 4:18 am >>>
Yes, you need the sensors made by masimo (if you already use masimo's in your nicu, you can use them). Do you want me to get the ordering info?

Sent from my BlackBerry Wireless Handheld

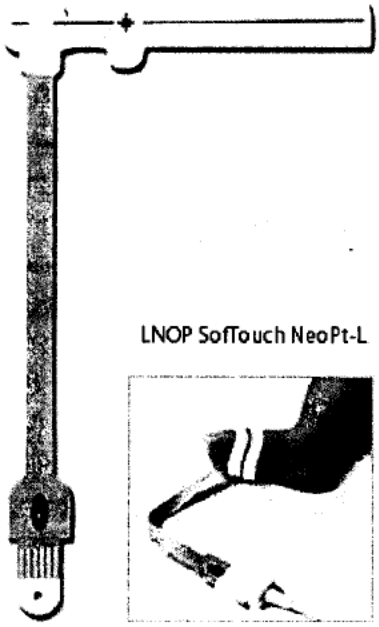
----- Original Message -----
From: Kristi Watterberg <KWatterberg@salud.unm.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Oct 18 17:34:01 2006
Subject: masimo sensors

Hi Rose. First technical question in starting up the SUPPORT study. We didn't get any sensors with the Masimos. Are we supposed to buy them before starting? (Connie's on vacation, so I don't have her available to tell me, if she knows)

thanks, Kristi

LNOP® NeoPt-L

neonatal preterm single patient sensor



LNOP SofTouch NeoPt-L

- Available in minimal adhesive or non-adhesive
- Recommended weight range: Less Than 1 Kg.
- Recommended monitoring site: Across the foot or alternatively across the palm & back of hand. Check site every 8 hours.

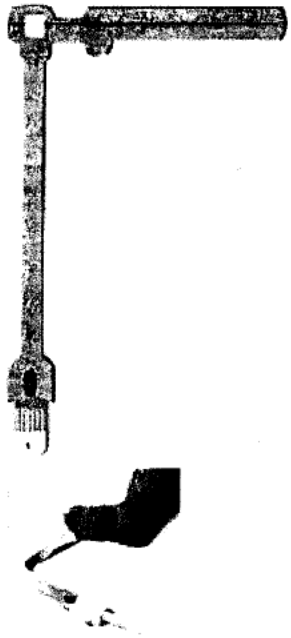
▶ Patent Information

	Neonatal	Pediatric	Adult
SofTouch Sensors	LNOP® NeoPt-L	LNOP® YI Multisite	LNOP® YI Multisite
	LNOP® NeoPt		
	LNOP® SofTouch NeoPt Bridge		
	LNOP® YI Multisite		

LNOP® sensors			LNCS® sensors		SofTouch™	specialty	patient
adhesive	reusable	multisite	adhesive	reusable	sensors	sensors	cables

LNOP® Neo-L

neonatal preterm single patient adhesive sensors



LNOP Neo-L/Neonatal

- Recommended weight range: Less Than 10 Kg.
- Recommended monitoring site: Across the foot or alternatively across the palm & back of hand.æ Check site every 8 hours.

▶ Patent Information

	Neonatal	Pediatric	Adult
LNOP Adhesive Sensors	LNOP® Néo	LNOP® Pdt	LNOP® Adt
	LNOP® Neo Bridge		
	LNOP® Neo-L	LNOP® Pdtx	LNOP® Adtx
	LNOP® Inf-L		

From:	Gantz, Marie
To:	Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Das, Abhik
Subject:	RE: SUPPORT
Date:	Tuesday, October 17, 2006 11:09:40 AM
Attachments:	SUPPORT Enrollment 10-2-06.doc SUPPORT FU windows Nov06-Apr07 10-13-06.rtf

Hi Rose,

Attached is the enrollment summary, with projections, that Neil presented at the SC meeting. I can update it if you would like, but only 5 more babies have been enrolled (to our knowledge) since the report was created.

I have also attached a list of the 100 SUPPORT infants whose follow-up windows open between November 2006 and April 2007.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 17, 2006 10:00 AM
To: Gantz, Marie
Cc: Das, Abhik
Subject: SUPPORT

HI,
Can you send me the recruitment table and projection of study completion? Also, the windows for FU for SUPORT babies.

Thanks
Rose

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

SUPPORT Enrollment as of October 2, 2006

Total Enrolled

	N	% of total (1310)
Enrolled	392	30%
With primary outcomes	236	18%

Enrollment by Center March 2006 – September 2006

Center	Mar-06	Apr-06	May-06	Jun-06	Jul-06	Aug-06	Sep-06	Total
3	5	6	4	2	1	3	1	22
4	0	1	1	3	0	3	1	9
5	2	1	0	1	0	0	1	5
9	0	3	2	4	2	1	1	13
11	0	0	0	1	1	7	2	11
12	0	0	4	2	1	0	2	9
13	0	0	1	1	0	1	0	3
14	0	2	2	7	3	0	4	18
15	0	1	1	0	2	0	2	6
16	0	0	0	6	6	7	0	19
18	0	5	1	3	1	5	2	17
19	0	0	1	3	3	1	0	8
21	1	0	0	0	0	0	0	1
25	0	0	0	0	0	0	2	2
Total	8	19	17	33	20	28	18	143
# Enrolling	3	7	9	11	9	8	10	
Avg/center	2.7	2.7	1.9	3.0	2.2	3.5	1.8	

Average Enrollment Per Center Per Month

Time period	Total enrolled	Average # of centers enrolling	Average per center per month
Apr06-Sept06	135	9	2.5
Jun06-Sept06	99	9.5	2.6

Months Needed to Enroll Remaining 918 Patients

Average per center per month	Number of centers enrolling								
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
2	58	51	46	42	39	36	33	31	29
2.5	46	41	37	34	31	29	27	25	23
3	39	34	31	28	26	24	22	21	20

SUPPORT FOLLOW-UP WINDOWS OPENING NOV06-APR07

Center	Follow-up order	Network ID	18 Month Follow-up Window Starting Date	18 Month Follow-up Window Ending Date
3:Case Western University	1	(b) (6)	01/23/07	06/07/07
	2		01/29/07	06/13/07
	3		02/11/07	06/26/07
	4		02/18/07	07/03/07
	5		02/19/07	07/04/07
	6		03/07/07	07/22/07
	7		03/11/07	07/26/07
	8		03/17/07	08/01/07
	9		04/02/07	08/17/07
	10		04/22/07	09/06/07
	11		04/25/07	09/09/07
4:University of Texas-Dallas	1	(b) (6)	04/12/07	08/27/07
	2	(b) (6)	04/29/07	09/13/07
8:University of Miami	1	(b) (6)	02/12/07	06/27/07
	2		02/21/07	07/06/07
	3		02/23/07	07/08/07
	4		04/06/07	08/21/07
	5		04/07/07	08/22/07
	6		04/22/07	09/06/07
	7		04/23/07	09/07/07
9:Emory University	1	(b) (6)	02/23/07	07/08/07
	2		03/15/07	07/30/07
	3		04/02/07	08/17/07
	4		04/08/07	08/23/07
	5		04/13/07	08/28/07
	6		04/14/07	08/29/07
11:University of Cincinnati	1	(b) (6)	12/07/06	04/22/07
	2		01/03/07	05/18/07
	3		02/22/07	07/07/07
	4		02/22/07	07/07/07
	5		03/16/07	07/31/07
	6		04/02/07	08/17/07
	7		04/02/07	08/17/07

SUPPORT FOLLOW-UP WINDOWS OPENING NOV06-APR07

Center	Follow-up order	Network ID	18 Month Follow-up Window Starting Date	18 Month Follow-up Window Ending Date
	8	(b) (6)	04/03/07	08/18/07
	9		04/12/07	08/27/07
	10		04/30/07	09/14/07
12:Indiana University	1	(b) (6)	12/22/06	05/07/07
	2		01/06/07	05/21/07
	3		02/10/07	06/25/07
	4		02/28/07	07/13/07
	5		03/14/07	07/29/07
	6		03/25/07	08/09/07
13:Yale University	1	(b) (6)	03/20/07	08/04/07
14:Brown University	1	(b) (6)	11/07/06	03/22/07
	2		12/25/06	05/10/07
	3		01/13/07	05/28/07
	4		01/20/07	06/04/07
	5		01/20/07	06/04/07
	6		02/27/07	07/12/07
	7		03/22/07	08/06/07
	8		03/26/07	08/10/07
	9		03/26/07	08/10/07
	10		04/05/07	08/20/07
	11		04/05/07	08/20/07
	12		04/15/07	08/30/07
	13		04/15/07	08/30/07
15:Stanford University	1	(b) (6)	02/06/07	06/21/07
	2		02/14/07	06/29/07
16:University of Alabama	1	(b) (6)	12/22/06	05/07/07
	2		01/11/07	05/26/07
	3		02/15/07	06/30/07
	4		02/24/07	07/09/07
	5		03/16/07	07/31/07
	6		03/16/07	07/31/07
	7		03/16/07	07/31/07
	8		03/19/07	08/03/07

SUPPORT FOLLOW-UP WINDOWS OPENING NOV06-APR07

Center	Follow-up order	Network ID	18 Month Follow-up Window Starting Date	18 Month Follow-up Window Ending Date
	9	(b) (6)	03/22/07	08/06/07
	10		03/26/07	08/10/07
	11		04/23/07	09/07/07
	12		04/29/07	09/13/07
	13		04/30/07	09/14/07
18:University of Tex-Houston	1	(b) (6)	12/26/06	05/11/07
	2		12/27/06	05/12/07
	3		12/27/06	05/12/07
	4		01/02/07	05/17/07
	5		01/07/07	05/22/07
	6		01/28/07	06/12/07
	7		02/19/07	07/04/07
	8		03/08/07	07/23/07
	9		03/28/07	08/12/07
	10		04/25/07	09/09/07
19:Duke University	1	(b) (6)	02/19/07	07/04/07
	2		03/15/07	07/30/07
	3		03/21/07	08/05/07
	4		04/15/07	08/30/07
22:University of California-San Diego	1	(b) (6)	11/24/06	04/08/07
	2		11/26/06	04/10/07
	3		12/02/06	04/17/07
	4		12/15/06	04/30/07
	5		02/10/07	06/25/07
	6		02/13/07	06/28/07
	7		02/16/07	07/01/07
	8		02/16/07	07/01/07
	9		02/22/07	07/07/07
	10		03/05/07	07/20/07
	11		03/09/07	07/24/07
	12		03/20/07	08/04/07
	13		03/25/07	08/09/07
	14		03/27/07	08/11/07
	15		04/02/07	08/17/07

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN Support Study Masimo oximeters
Date: Tuesday, October 17, 2006 10:30:20 AM

Hi,
Did Maribeth Sayre ever respond to you (please see below). I asked Tufts and UAB to send back the oximeters with the incorrect histogram but have no documentation from Masimo to confirm whether the oximeters were correctly blinded; Wade did test them and said they were properly skewed.
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 12:09 PM
To: Maribeth Sayre
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: NICHD NRN Support Study Masimo oximeters

HI,
Can you let us know if these were correctly blinded?
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: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Tuesday, September 19, 2006 1:41 PM
To: Zaterka-Baxter, Kristin; Chris Novak; Vicki Bishop; George Yaghnam
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Study Masimo oximeters

Hi Kristin,

The easiest way to test the oximeters is to set the simulator at 90%.
The oximeter should read either 93 or 87.
I don't know why these oximeters have the standard histogram instead of the SUPPORT histogram.
The good news is that our process has changed, so this should not be a problem in the future.
To change the histograms, please send the oximeters back to Irvine. You will need to call for a RMA#,
fill out the attached form noting that these are masked oximeters that need to have the

histogram changed to the SUPPORT histogram, and send to the attention of Chris Novak. Masimo will pay the shipping charges.

Thanks,
Maribeth

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, September 18, 2006 10:37 AM
To: Maribeth Sayre; Chris Novak; Vicki Bishop
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: NICHD NRN Support Study Masimo oximeters

Hi Marybeth,

Please find below masimo oximeter serial numbers of instruments found recently to have seemingly normal histogram ranges instead of the skewed ranges required for the masked NRN Support study. These are not new oximeters but instead have been recently moved from our Miami site to the University of Alabama site where the histogram ranges were notice to be different than what was viewed on their current oximeters of the same color code. We're not sure if this has affected the data in any way or if it's something that's possibly just incorrect on the visual screen. We are in the process of trying to test one of these oximeters with an oximeter simulator but this will not take place until tomorrow at the earliest.

These are the oximeters that were originally sent to the University of Miami on April 7, 2005.

317219
317312
317363
317393
317408
317420
317431
317443

These are the histogram ranges on the Miami Masimo's and our UCSD study coordinator has told me these are also the standard for Masimo's off the shelf.

96-100%
91-95%
86-90%
81-85%
<85%

Please let me know if you need further information to look into this matter; I'd be happy to send you whatever is needed.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762

kzaterka@rti.org

From: Das, Abhik
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Susie Buchter; Barbara Stoll; anthony_piazza@oz.ped.emory.edu; ellen_hale@oz.ped.emory.edu; Poole, W. Kenneth; Gantz, Marie
Subject: RE: SUPPORT QUESTION
Date: Monday, October 16, 2006 4:27:48 PM

I still think one is required because treatment/intervention commenced before randomization, and no exceptions covering such situations is noted in the protocol or manual. This is not meant to be punitive or anything like that; just a matter of record keeping.

Thanks

Abhik

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, October 16, 2006 4:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Susie Buchter; Barbara Stoll; anthony_piazza@oz.ped.emory.edu; ellen_hale@oz.ped.emory.edu
Subject: RE: SUPPORT QUESTION

HI Rose
From our previous conversation Abhik felt that a violation was required because of the timing of the pulling of the card – ie Not prior to delivery. There is no actual protocol violation here in terms of the study procedures. I question whether a precipitous delivery is grounds for a protocol violation. I think that the team is acting appropriately to enter a consented infant and would favor NOT completing a protocol violation. Perhaps there should be an explanation attached.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 16, 2006 1:16 PM
To: Neil Finer; Das, Abhik
Cc: Susie Buchter; Barbara Stoll; anthony_piazza@oz.ped.emory.edu; ellen_hale@oz.ped.emory.edu
Subject: SUPPORT QUESTION

HI,
Ellen called me about an hour ago – a previously consented mother came in and precipitously delivered. The baby was stabilized on NCPAP and Ellen asked me at about 25 minutes of age if the child could still be enrolled – I told her absolutely YES – the child randomized to CPAP.
DO we fill out anything if the card is not pulled prior to delivery and this situation of the card matching the therapy for CPAP occurs??

Also, we are getting 4 oximeters from Duke so that Emory has enough equipment to enroll all of the moms that they have consented!!! Keep up the good work!!!
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: Zaterka-Baxter, Kristin
Cc: ALaptook@wihri.org; Roger Faix; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Suggested Support form revisions
Date: Monday, October 16, 2006 3:46:23 PM

Hi Kris
The only responses that I received regarding the form changes were from Abbot and Roger. They felt that adding a comment to the current SUPP04 would be adequate and avoid making more changes. I agree.
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, September 28, 2006 10:33 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; Walsh, Michele; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; Wade Rich; Petrie, Carolyn
Cc: Auman, Jeanette O.; Pickett, James
Subject: Suggested Support form revisions

Dear Support Subcommittee Members,

During the last Steering Committee meeting in July and on subsequent coordinator conference calls, several revisions were suggested for Support study forms Supp04, Supp05, Supp05A, Supp06, Supp08, and Supp12 (new). Over the last several months these revisions have been refined by a group of study coordinator with some comments and suggestions from Dr. Finer and Wade Rich. These drafts are attached for your review. We would like to discuss these suggestions during the upcoming Steering Committee meeting in October. Once discussions have concluded and if the committee finds the changes appropriate, the manual will be updated accordingly. Below please find a brief description of all changes and attached are copies of the draft forms with these changes highlighted.

Supp04:
1. It has been suggested that question **B.2** should be renumbered to subquestion B.1.**d.** Question B.2 *"Was a blood gas done within 30 minutes prior to intubation,* is only required to be answer if Q.B.1= yes *"Was the infant intubated for the first time within the first 14 days after admission to the NICU",* otherwise Q.B.2 is skipped, along with Q.B.1.a, b, and c. This revision has been drafted and would require reprogramming and a new forms version. An option would be to add a clarifying statement to Q.B.2; *"complete this question only if Q.B.1 = yes"* which would require no DMS changes.

Supp05:
1. We've re-worked this form reformatting and renumbering to hopefully make it less confusing. All data points have remained the same with two exceptions; question 14 and 14a (about replacement oximeters) have been deleted because the new Supp12 will capture all oximeter replacement data, and the addition of code '9' (Mode of Support) to document "No support all day and off the study oximeter".

Supp05A
1. We've revised the instructions on this form to clarify its intended use as follows:
Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

2. We've deleted the Section B title "Intubated/Extubated Information (For NICU Only)" as this was a carry over from the old form and is no longer needed. This has prompted the subsequent renumbering of the form.

3. Previous Q.1.a (now Q.3.a) re. intubation has been revised removing the 'if yes' text and placing the text where it is now clear that both Q.3.a and 3.b must be answered if Q.3 = yes.

4. Based on discussions of relevant blood gas data in relation to intubation/extubation events, Dr. Finer has suggested that the pH, PCO2 should be reported if within 6 hours prior to the event (as stated currently on the Supp07 form). We've added question 'b.1', renumbered 'pH' and 'PCO2' to Q.b.1.a and Q.b.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

5. Previous Q.2.a (now Q.4.a) re. extubation has also been revised to by removing the 'if yes' text and placing the text where it is now clear that both Q.4.a and 4.b must be answered.

6. As in explanation #4 above, we've added question 'c.1', renumbered 'pH' and 'PCO2' to Q.c.1.a and Q.c.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

7. Previous Q.3 and 3a have been deleted because the new Supp12 will capture all oximeter replacement data

Supp06
Two types of protocol deviations have been added as options to select as listed below. We have also renumbered the 'Other' option to code '99' for ease of data programming:
Code 11. Incorrect randomization card select (incorrect gestational age group)
Code 12. Postnatal Steroids given for BPD/CLD within 21 days of life.

Supp08
Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting in July. The data that is intended to be captured are any AEs within the first 14 days of life only. The statement "*or prior to study status*" has been removed from the instructions on the form. Question 1 has been deleted and AE #1 (Air leak) has been revised by removing the statement "*in the first 14 days*"

New Supp12
This new form will capture all study oximeter replacement data throughout the study period from initiation to 36 weeks or status.

Your comments and suggestions are greatly appreciated.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From:	Kurt Schibler
To:	Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc:	Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject:	Re: SUPPORT FU
Date:	Monday, October 16, 2006 11:03:07 AM

Hi Rose,
If the Follow-up PI's are in agreement with this plan, I vote YES to perform the Bayley III cognitive, receptive, and expressive language elements and not gross and fine motor elements that will be captured with the neuro exam.
Thanks,
Kurt

Kurt Schibler, MD
Associate Professor of Pediatrics
Division of Neonatology
Cincinnati Children's Hospital
3333 Burnet Avenue
Cincinnati, Ohio 45229-3972
TEL: 513-636-3972
FAX: 513-636-4404
Pager: 513-736-(b)
E-mail: kurt.schibler@cchmc.org On 10/13/06 9:52 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
> The follow up PI's have discussed the pros and cons of Bayley II and III exams
> for SUPPORT FU. They have voted unanimously to perform the Bayley III to
> include cognitive, receptive and expressive language elements and NOT to
> include gross and fine motor elements as these are duplicative in the neuro
> exam. There was also a vote to consider changing the timing of the window -
> 18-22 months (11 votes) to 24-28 months (4 votes) as the Bayley III is a
> little easier as children get a little older.
>
> Bayley III certifications videos are due by October 31. If we do not have the
> videos by Thanksgiving from the 15 sites whose windows will open in late 2006
> or early 2007, this will need to come back to the group for reconsideration (I
> will send out weekly reminders in November to sites with missing videos).
>
> The FU PI's are committed to instituting the Bayley III at the sites despite
> the concerns from the Gold Standard examiners raised over the last two days.
>
> Let me know if the subcommittee is ok with this by Monday, October 16. Thanks
> for your patience and valuable contribution to the discussion!
> Rose
> ---
> Sent from my BlackBerry Wireless Handheld

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]; Michele.Walsh@UHhospitals.org; nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: RE: SUPPORT FU
Date: Friday, October 13, 2006 7:41:05 PM

Rose
After listening to the issues and the comments of the F/U PIs I think the proposal that has been put forth is very reasonable. AL

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 13, 2006 11:54 AM
To: Michele.Walsh@UHhospitals.org; nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; Abbot Laptook; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: Re: SUPPORT FU

Please note - we are NOT to include gross and fine motor elements as these are duplicative in the neuro exam.
The Bayley III will take less than one hour in this fashion.
More discussion is welcome!
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Walsh, Michele <Michele.Walsh@UHhospitals.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; alaptook@wihri.org <alaptook@wihri.org>; adas@rti.org <adas@rti.org>; poo@rti.org <poo@rti.org>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; bradley.yoder@hsc.utah.edu <bradley.yoder@hsc.utah.edu>
Cc: Timothy_Stevens@URMC.Rochester.edu <Timothy_Stevens@URMC.Rochester.edu>; srhintz@stanford.edu <srhintz@stanford.edu>; petrie@rti.org <petrie@rti.org>
Sent: Fri Oct 13 11:48:24 2006
Subject: RE: SUPPORT FU

After listening to the concerns of the Gold Standard examiners about the considerable longer length of time for the Bayley III and the estimate that only 75% will get a score: I am gravely concerned about changing to the Bayley III. Since the intent of the trial is to compare two treatments, I think it is less important to understand what domain the deficits are in: something that I understand is of vital interest to those doing neonatal fu like the 'generic FU program'. I think our primary goal in this trial is to compare the treatments and ensure that

those in one sat range vs the other are not harmed. I understand that it is difficult to

have two evaluations going on at the same time- but for SUPPORT I do NOT agree with changing to the Bayley III. WE can switch when SUPPORT is completed: yet another reason to finish SUPPORT expeditiously- perhaps by increasing the number of enrolling centers.
Michele

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 13, 2006 9:52 AM
To: nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: SUPPORT FU

Hi,
The follow up PI's have discussed the pros and cons of Bayley II and III exams for SUPPORT FU. They have voted unanimously to perform the Bayley III to include cognitive, receptive and expressive language elements and NOT to include gross and fine motor elements as these are duplicative in the neuro exam. There was also a vote to consider changing the timing of the window - 18-22 months (11 votes) to 24-28 months (4 votes) as the Bayley III is a little easier as children get a little older.

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Let me know if the subcommittee is ok with this by Monday, October 16.
Thanks for your patience and valuable contribution to the discussion!
Rose

Sent from my BlackBerry Wireless Handheld

specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From:	Neil Finer
To:	Abbot Laptook
Cc:	kzaterka@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; mcw3@po.cwru.edu; kurt.schibler@cchmc.org; adas@rti.org; WCarlo@PEDS.UAB.edu; Roger.Faix@hsc.utah.edu; Wade Rich; petrie@rti.org; Wade Rich
Subject:	RE: Support forms
Date:	Friday, October 13, 2006 6:50:41 PM

Thanks Abbot
Neil

From: Abbot Laptook [mailto:ALaptook@WIHRI.org]
Sent: Friday, October 13, 2006 2:12 PM
To: Neil Finer
Cc: kzaterka@rti.org; HigginsR@mail.nih.gov; mcw3@po.cwru.edu; kurt.schibler@cchmc.org; adas@rti.org; WCarlo@PEDS.UAB.edu; Roger.Faix@hsc.utah.edu; Wade Rich; petrie@rti.org
Subject: Support forms

Neil
The changes that were suggested to the forms look fine to me. With regard to supp04, I would go with the addition of the clarifying statement so that no DMS changes are needed. Although I do understand the concern of changing forms and the difficulty this may pose when you collate data, I think the overall benefits of the changes to the coordinators will enhance accurate data collection. AL

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT FU
Date: Friday, October 13, 2006 11:51:08 AM

Can you clarify that we are removing the Motor to decrease time and will capture the info on the neuro.

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Friday, October 13, 2006 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; Das, Abhik; Poole, W. Kenneth; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; Petrie, Carolyn
Subject: RE: SUPPORT FU

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deficits are in: something that I understand is of vital interest to those
doing neonatal fu like the 'generic FU program'. I think our primary goal in this trial is to compare the treatments and ensure that those in one sat
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have two evaluations going on at the same time- but for SUPPORT I do NOT agree with changing to the Bayley III. WE can switch when SUPPORT is completed: yet another reason to finish SUPPORT expeditiously- perhaps by
increasing the number of enrolling centers.
Michele

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 13, 2006 9:52 AM
To: nfiner@ucsd.edu; mcw3@po.cwru.edu; wcarlo@peds.uab.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: SUPPORT FU

Hi,
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of the window - 18-22 months (11 votes) to 24-28 months (4 votes) as the Bayley III is a little easier as children get a little older.

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Let me know if the subcommittee is ok with this by Monday, October 16. Thanks for your patience and valuable contribution to the discussion!
Rose

Sent from my BlackBerry Wireless Handheld

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mcw3@po.CWRU.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; adas@rti.org; poo@rti.org; roger.faix@hsc.utah.edu; bradley.yoder@hsc.utah.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; srhintz@stanford.edu; petrie@rti.org
Subject: Re: SUPPORT FU
Date: Friday, October 13, 2006 10:00:53 AM

Rose and all:

I am sure the FU PIs considered all pros and cons as we were part of some of it.

I agree with their vote.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; alaptook@wihri.org <alaptook@wihri.org>; adas@rti.org <adas@rti.org>; poo@rti.org <poo@rti.org>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; bradley.yoder@hsc.utah.edu <bradley.yoder@hsc.utah.edu>
CC: Timothy_Stevens@URMC.Rochester.edu <Timothy_Stevens@URMC.Rochester.edu>; srhintz@stanford.edu <srhintz@stanford.edu>; petrie@rti.org <petrie@rti.org>
Sent: Fri Oct 13 08:52:22 2006
Subject: SUPPORT FU

Hi,
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Let me know if the subcommittee is ok with this by Monday, October 16. Thanks for your patience and valuable contribution to the discussion!
Rose

Sent from my BlackBerry Wireless Handheld

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT Minutes
Date: Thursday, October 12, 2006 7:43:24 AM
Attachments: Support Meeting Minutes.ppt

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, October 11, 2006 8:03 PM
To: Petrie, Carolyn
Cc: higginsr@mail.nih.gov
Subject: SUPPORT Minutes

Hi Carolyn
Here is my report
Talk to you in the morning
Be well
Neil

SUPPORT Subcommittee Committee Minutes – Oct 10 2006

- Reviewed Enrollments – 392 to date
- Projection that study will require another 29 months
- Reviewed Adverse Events – Lower than GDB 2002-2004
- Oximeter data – sites sent formatted report
- Discussion of Secondaries
- Other Issues

SUPPORT Enrollment

	N	% of total (1310)
Enrolled	392	30%
With primary outcomes	236	18%

Time period	Total enrolled	Average # of centers enrolling	Average per center per month
Apr06-Sept06	135	9	2.5
Jun06-Sept06	99	9.5	2.6

Support Enrollment

Average per center per month	Number of centers enrolling								
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
2	58	51	46	42	39	36	33	31	29
2.5	46	41	37	34	31	29	27	25	23
3	39	34	31	28	26	24	22	21	20

Support Adverse Events

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest Compressions or epinephrine in DR	5.7	7.7	4.2
Air leak	6.5	8.3	5.3
Pulmonary hemorrhage	6.0	8.3	4.3
Severe IVH (grades III-IV)	11.5	16.7	7.6

GDB Cohort 2002-04			
Chest Compressions or epinephrine in DR	11.2	13.2	9.1
Air leak	8.2	11.0	6.1
Pulmonary hemorrhage	9.0	12.3	6.5
Severe IVH (grades III-IV)	16.9	24.2	11.7

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Oximeter Downloads – Format of Site Report

Dates	Time on supplemental oxygen	Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Through Nov05	Days of life 1-14	XX	1885	28.9	14.9	77.2	7.9
		All centers	25306	37.6	9.4	79.2	11.4
	> 14 days - 36 wks	XX	18215	20.9	17.3	66.6	16.1
		All centers	158594	28.1	11.9	69.5	18.6
Mar06-Aug06	Days of life 1-14	XX	1928	48.1	6.3	84.5	9.2
		All centers	9901	43.3	7.2	82.3	10.5
	> 14 days- 36 wks	XX	9388	37.3	11.9	73.2	14.9
		All centers	40940	33.2	10.6	72.7	16.7

SUPPORT Secondary Studies: MRI Secondary

- **MRI – 13 sites are moving toward enrollment. 11 have IRB approval**
- **8 – Separate Consent – 5 Imbedded**
- **Enrollment is 81 infants. 52 are completed.**
- **Still possible to enroll 500 infants**

SUPPORT Secondary Studies: Breathing Outcomes

- **153 enrolled of 302 in follow-up**
- **All centers enrolling in Support are doing this study.**
- **Awaiting detailed report from PI.**

Secondary Studies: Antenatal Consent

- 636 Screened, 510 Approached, 151 Enrolled
- Target is 50 Delivered in window per site

Secondary Studies: Growth

- **52 enrolled to date**

SUPPORT : Other Issues

- **Discussed Bayley III – Follow-up PIs to review**
  - Consensus was to stay with Bayley II
- **Missing ROP forms – Marie is going to send data to sites regarding missing information at > 50 weeks**

SUPPORT Study

- **Congratulations to New Sites for great start-up**
- **Thanks to all the PI's and Especially Coordinators for all their efforts**

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT SAE
Date: Tuesday, October 10, 2006 3:34:32 PM

Rose,
Our other twin in SUPPORT (b) (6) this afternoon (since I sent the last email). This infant was extremely ill and had Gr IV IVH and care was withdrawn. Cause of death was not related to the study. MedWatch and summary will be coming.
Ellen

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT SAE
Date: Tuesday, October 10, 2006 1:20:07 PM

Rose,
It does not look so good for the other twin in the SUPPORT study. That one now has a grade IV IVH and was made DNR yesterday. I'm in my office now.
Ellen

From: Petrie, Carolyn
To: Navarrete, Cristina
Cc: sduara@miami.edu; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu; Zaterka-Baxter, Kristin; Petrie, Carolyn
Subject: RE: SUPPORT subcommittee call
Date: Tuesday, October 10, 2006 8:48:10 AM

Cristina-

Please touch base with Dr. Finer, cc'd in this email before the meeting.

We are scheduled to meet tomorrow (Wed, Oct. 11) 11:00-12:00pm ET

To join the call,

Dial Toll Free, **866-675-**(b) (6)
Passcode: (b) (6)

Thank you!!!

Carolyn

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Monday, October 09, 2006 6:14 PM
To: Petrie, Carolyn
Subject: RE: SUPPORT subcommittee call

Hi! I am on service this month and make rounds in the morning. I'll try to make time though. Please tell me what number to call and if there is anything I should prepare...
Thanks

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Mon 10/9/2006 1:02 PM
To: Navarrete, Cristina
Cc: sduara@miami.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT subcommittee call

Cristina-

Are you available to speak with the SUPPORT subcommittee this Wednesday 11:00am-12:00pm ET?

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: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: FW: support subject death
Date: Tuesday, October 10, 2006 8:46:01 AM

-----Original Message-----
From: Tate, Patti L [mailto:Patti.L.Tate@uth.tmc.edu]
Sent: Monday, October 09, 2006 5:22 PM
To: hittinw4@mqil.nih.gov
Cc: Petrie, Carolyn
Subject: support subject death

Notification of the death o(b) (6) who was enrolled in the Support Study. The death was not related to the study.
Medwatch to follow awaiting completed death note and possible autopsy.
Thanks Patti

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Susie Buchter
Subject: SUPPORT SAE
Date: Monday, October 09, 2006 1:26:01 PM

Dear Rose,

We are reporting a death in the SUPPORT study (death not related to study). Baby (b) (6) died (b) (6) at 1707. We will fax the Medwatch and summary today.

Ellen

From:	Petrie, Carolyn
To:	Scott, Francilia (NIH/OD) [C]
Cc:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	FW: Oximeter data for the SUPPORT Trial
Date:	Friday, October 06, 2006 2:28:19 PM
Attachments:	SUPPORT Adverse Events 10-2-06.doc SUPPORT Enrollment 10-2-06.doc SUPPORT Protocol Deviations 10-2-06.doc SUPPORT Protocol Deviations by center 10-2-06.doc

---

Can you make 15 copies?

Thank you!!

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, October 05, 2006 3:29 PM
To: Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; Das, Abhik; Gantz, Marie; Poole, W. Kenneth; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich; Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
I would like to share these documents with you and propose that we discuss at the upcoming Steering Committee. Please review the form changes sent to you by Kris
I would propose the following agenda
1. Current status of enrollments
2. Review of Adverse Events
3. Review Oximeter data and site data
4. Discussion of Secondaries- Susan Hintz - MRI
- Tim Stevens - Breathing Outcomes

5. Form Changes
6. Other issues
Please let me know any additions etc.
Regards
Neil

Percent of SUPPORT infants with selected adverse events*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	5.7	7.7	4.2
Air leak	6.5	8.3	5.3
Pulmonary hemorrhage	6.0	8.3	4.3
Severe IVH (grades III-IV)	11.5	16.7	7.6

Note: Table includes SUPPORT infants who are still hospitalized and at risk for additional AEs

Percent of GDB infants with selected adverse events and range across NRN centers* (Includes infants born at NRN centers at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8

*Denominator for chest compressions is number of infants with delivery room information, denominator for air leak and pulmonary hemorrhage is number of infants who survived 12 hours, denominator for severe IVH is number of infants with head ultrasound.

SUPPORT Enrollment as of October 2, 2006

Total Enrolled

	N	% of total (1310)
Enrolled	392	30%
With primary outcomes	236	18%

Enrollment by Center March 2006 – September 2006

Center	Mar-06	Apr-06	May-06	Jun-06	Jul-06	Aug-06	Sep-06	Total
3	5	6	4	2	1	3	1	22
4	0	1	1	3	0	3	1	9
5	2	1	0	1	0	0	1	5
9	0	3	2	4	2	1	1	13
11	0	0	0	1	1	7	2	11
12	0	0	4	2	1	0	2	9
13	0	0	1	1	0	1	0	3
14	0	2	2	7	3	0	4	18
15	0	1	1	0	2	0	2	6
16	0	0	0	6	6	7	0	19
18	0	5	1	3	1	5	2	17
19	0	0	1	3	3	1	0	8
21	1	0	0	0	0	0	0	1
25	0	0	0	0	0	0	2	2
Total	8	19	17	33	20	28	18	143
# Enrolling	3	7	9	11	9	8	10	
Avg/center	2.7	2.7	1.9	3.0	2.2	3.5	1.8	

Average Enrollment Per Center Per Month

Time period	Total enrolled	Average # of centers enrolling	Average per center per month
Apr06-Sept06	135	9	2.5
Jun06-Sept06	99	9.5	2.6

Months Needed to Enroll Remaining 918 Patients

Average per center per month	Number of centers enrolling								
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
2	58	51	46	42	39	36	33	31	29
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SUPPORT Trial Protocol Deviations Reported as of 10/2/2006

Type of protocol deviation	Number
CPAP not initiated if required by protocol	1
Surfactant not given in the first hour	6
Oximeter not started within 2 hours	5
Infant placed on study oximeter for incorrect treatment	3
Failure to use study oximeter at times required by protocol	17
Non-study (unmasked) oximeter used at same time as study oximeter	2
NSIMV initiated in infant not previously intubated	2
Extubation (excluding unplanned) for other than study criteria	3
Failure to extubate CPAP infant if all criteria met	3
Failure to extubate surfactant infant if all criteria met	1
High flow nasal cannula used within first 14 days of life	9
Infant received postnatal steroids in first 21 days of life	8
Head ultrasound done outside 4-21 day windown	1
Consent errors	2
Randomization errors	6
Other	2
Total	71

Type of protocol deviation	Number
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	3	4	8	9	11	12	14	16	18	19	20	21	22	
CPAP not initiated if required by protocol								1						1
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Infant placed on study oximeter for incorrect treatment	1		1					1						3
Failure to use study oximeter at times required by protocol	5	2			2		3	2	1	1	1			17
Non-study (unmasked) oximeter used at same time as study oxim.					1							1		2
NSIMV initiated in infant not previously intubated		1						1						2
Extubation (excluding unplanned) for other than study criteria					1			1				1		3
Failure to extubate CPAP infant if all criteria met		1											2	3
Failure to extubate surfactant infant if all criteria met					1									1
High flow nasal cannula used within first 14 days of life				1	4		2		1				1	9
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Head ultrasound done outside 4-21 day window								1						1
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Randomization errors		1		1					1	1	2			6
Other					1		1							2
Total	8	6	1	2	13	1	9	12	5	2	3	2	7	71

From:	Neil Finer
To:	Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Petrie, Carolyn; kzaterka@rti.org
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Thursday, October 05, 2006 3:29:11 PM
Attachments:	SUPPORT Adverse Events 10-2-06.doc SUPPORT Enrollment 10-2-06.doc SUPPORT Protocol Deviations 10-2-06.doc SUPPORT Protocol Deviations by center 10-2-06.doc

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12	0	0	4	2	1	0	2	9
13	0	0	1	1	0	1	0	3
14	0	2	2	7	3	0	4	18
15	0	1	1	0	2	0	2	6
16	0	0	0	6	6	7	0	19
18	0	5	1	3	1	5	2	17
19	0	0	1	3	3	1	0	8
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Surfactant not given in the first hour	2				2	1	1							6
Oximeter not started within 2 hours					1			3	1					5
Infant placed on study oximeter for incorrect treatment	1		1					1						3
Failure to use study oximeter at times required by protocol	5	2			2		3	2	1	1	1			17
Non-study (unmasked) oximeter used at same time as study oxim.					1							1		2
NSIMV initiated in infant not previously intubated		1						1						2
Extubation (excluding unplanned) for other than study criteria					1			1				1		3
Failure to extubate CPAP infant if all criteria met		1											2	3
Failure to extubate surfactant infant if all criteria met					1									1
High flow nasal cannula used within first 14 days of life				1	4		2		1				1	9
Infant received postnatal steroids in first 21 days of life							2	2					4	8
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Consent errors		1							1					2
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Other					1		1							2
Total	8	6	1	2	13	1	9	12	5	2	3	2	7	71

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; roger.faix@hsc.utah.edu
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Wednesday, October 04, 2006 10:40:07 PM

Roger
You guys Rock!!!!
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 03, 2006 3:55 PM
To: roger.faix@hsc.utah.edu
Cc: Neil Finer
Subject: Re: SUPPORT MRI SECONDARY STUDY

Terrific!!
Thanks
For the update!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Roger Faix <Roger.Faix@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Oct 03 18:13:28 2006
Subject: Re: SUPPORT MRI SECONDARY STUDY

Hi Rose! Neuroimaging consent is embedded in SUPPORT consent, so all of our enrollees (5 so far, I believe) have consented to participate in the neuroimaging as well. We have not yet performed any of the study-related MRIs yet (first one will be in late November, as I recall).

Roger

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 09/29/06 10:11 AM >>>
Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary by OCTOBER 3:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

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: Susan Hintz
To: nxs5@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mcw3@case.edu
Subject: Fwd: RE: SUPPORT MRI SECONDARY STUDY
Date: Wednesday, October 04, 2006 4:14:17 PM

Thanks for the update Nancy! Good luck on continued enrollment -

Susan

Susan R. Hintz, M.D., M.S. Epi
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

Delivered-To: srhintz@stanford.edu

From: "Nancy Newman" <nxs5@case.edu>
To: "'Higgins, Rosemary \(NIH/NICHD\) [E]'" <higginsr@mail.nih.gov>,

<mcw3@case.edu>
Cc: "'Susan Hintz'" <srhintz@stanford.edu>
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Wed, 4 Oct 2006 11:37:48 -0400
Thread-index: Acbj4fAL5zHOTF1iRBiuJzoDbMhKQgDRWOVgAChruWA=

Hi All-

We have consented 12 SUPPORT patients for the MRI secondary. 2 kids expired (1 had only early HUS, other had early & late HUS but was too ill to go to MRI suite). 8 kids have early & late HUS & MRIs - the requests are in to radiology for copies of MRIs (on CD) and HUS (films). Two additional infants are not yet 35 weeksŠŠŠŠŠ.NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 03, 2006 4:08 PM
To: mcw3@case.edu; Nancy Newman
Cc: Susan Hintz
Subject: FW: SUPPORT MRI SECONDARY STUDY

Hi,

Can you folks send us an update on the MRI secondary study?
Thanks

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 29, 2006 12:12 PM
Cc: 'susan.hintz@stanford.edu'
Subject: SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary **by OCTOBER 3**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

Rosemary D. Higgins, M.D.

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301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

--

From: Monica Collins
To: Monica Collins; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Wednesday, October 04, 2006 11:49:31 AM

Rose,
We have had 18 eligible. Out of those 15 consented (1 was transferred without consent, one died without consent, and the third refused), we have completed 7. The rest are still eligible.
Monica

From: Monica Collins
Sent: Tue 10/3/2006 7:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT MRI SECONDARY STUDY

Rose,
I can send you the actual numbers tomorrow. We have done about 5 MRIs (but I will give you the actual numbers tomorrow).
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 10/3/2006 3:05 PM
To: Wally Carlo, M.D.; Monica Collins
Cc: Susan Hintz
Subject: FW: SUPPORT MRI SECONDARY STUDY

Hi,
Can you send us the requested info?
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, September 29, 2006 12:12 PM
Cc: 'susan.hintz@stanford.edu'
Subject: SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary **by OCTOBER 3**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

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: Susan Hintz
To: Roger.Faix@hsc.utah.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Fw: SUPPORT MRI SECONDARY STUDY
Date: Tuesday, October 03, 2006 7:28:13 PM

Roger,

Thanks so much for the update! Congratulations on your enrollment!

Susan

Susan R. Hintz, M.D., M.S. Epi
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

>Delivered-To: srhintz@stanford.edu
>Subject: Fw: SUPPORT MRI SECONDARY STUDY
>Date: Tue, 3 Oct 2006 19:19:39 -0400
>Thread-Topic: SUPPORT MRI SECONDARY STUDY
>Thread-Index: AcbnOTPACVDuB/E9RvWQpfFQbMZg0QACTUGX
>From: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
>To: <srhintz@stanford.edu>
>X-OriginalArrivalTime: 03 Oct 2006 23:19:40.0147 (UTC)
>FILETIME=[6693FC30:01C6E742]
>
>FYI
>----------
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
> >From: Roger Faix <Roger.Faix@hsc.utah.edu>
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Sent: Tue Oct 03 18:13:28 2006
>Subject: Re: SUPPORT MRI SECONDARY STUDY
>
>Hi Rose! Neuroimaging consent is embedded in SUPPORT consent, so all of
>our enrollees (5 so far, I believe) have consented to participate in the
>neuroimaging as well. We have not yet performed any of the study-related
>MRIs yet (first one will be in late November, as I recall).
>
>Roger
>
>>>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
>09/29/06 10:11 AM >>>
>Please respond to the following questions pertaining to the SUPPORT
>Neuroimaging secondary by OCTOBER 3:
>
>

>
>How many patients have been enrolled in the Neuroimaging secondary at
>your site?
>
>
>
>If your site has enrolled patients, has your site performed any
>study-related brain MRI's or cranial US yet?
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>
>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: Petrie, Carolyn; nfiner@ucsd.edu; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; vineet.bhandari@yale.edu; harris.jacobs@yale.edu; monica.konstantino@yale.edu; richard.ehrenkranz@yale.edu; Poole, W. Kenneth; Zaterka-Baxter, Kristin
Cc: fmartinez@ucsd.edu
Subject: RE: Yale SUPPORT call
Date: Tuesday, October 03, 2006 5:17:27 PM

Reminder for tomorrow's call.

From: Petrie, Carolyn
Sent: Tuesday, September 26, 2006 4:02 PM
To: 'nfiner@ucsd.edu'; 'Wade Rich'; 'higginsr@mail.nih.gov'; Das, Abhik; ' (vineet.bhandari@yale.edu)'; 'harris.jacobs@yale.edu'; 'monica.konstantino@yale.edu'; 'richard.ehrenkranz@yale.edu'; Poole, W. Kenneth; Zaterka-Baxter, Kristin
Cc: 'Fernando Martinez (fmartinez@ucsd.edu)'; Petrie, Carolyn
Subject: Yale SUPPORT call

The conference call to discuss the SUPPORT study with Yale is scheduled for

Wednesday, October 4th
11:00am Eastern Time (8:00am Pacific Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

Please note that we wish to include both JoAnn Poulsen, RN and Janet Taft, RN but I do not have their email addresses (from the NRN website).

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

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: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support sites not participating
Date: Tuesday, October 03, 2006 5:01:07 PM

I know; but I dont think it has percolated!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 03, 2006 5:00 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: Support sites not participating

I think I had also stated this at the last steering committee meeting.

Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, October 03, 2006 4:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: RE: Support sites not participating

I agree completely. For Wayne State and SUPPORT, we can ask Marie to look at the eligibles by site (within that center) to answer Neil's question about the percentage breakdown between the 2 sites.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 03, 2006 4:56 PM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: RE: Support sites not participating

They need to be left in – the sites competed in peer review based on these additional sites and it is not fair for them to simply say they are not going to recruit at one or more sites.

Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, October 03, 2006 4:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support sites not participating

Currently, I think, we're not including GDB eligible's for support from specific sites not participating in support if we're aware they're not participating. Should we be taking them out or leaving them in even though those some sites aren't participating in Support.

Thanks

Kris

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: GDB%/Support
Date: Tuesday, October 03, 2006 4:54:59 PM

Please see below.
Thanks,

Kris

From: Auman, Jeanette O.
Sent: Tuesday, October 03, 2006 4:53 PM
To: Zaterka-Baxter, Kristin
Subject: RE: GDB%/Support

Correct. If they have a SUPP01 for a patient with a DOB that's their start date and it only looks at GDB records from that point forward. If there's no SUPP01, they don't have a start date.

From: Zaterka-Baxter, Kristin
Sent: Tuesday, October 03, 2006 4:50 PM
To: Auman, Jeanette O.
Subject: GDB%/Support
Importance: High

Currently, I think, we're not including GDB eligible's for support from specific sites not participating in support if we're aware they're not participating.
Right?

Kris

From: Mcdavid, Georgia E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: oximeters
Date: Tuesday, October 03, 2006 2:39:55 PM

Thank you Rose!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 03, 2006 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; nxs5@po.cwru.edu; MCollins@peds.uab.edu; AHensman@WIHRI.org; scosby@peds.uab.edu; mbball@leland.stanford.edu; auten002@mc.duke.edu
Cc: kzaterka@rti.org; Tyson, Jon E; Morris, Brenda H; Mcdavid, Georgia E; petrie@rti.org; neil finer
Subject: RE: oximeters

HI,
Stanford will send 2 orange oximeters to complete the request!!!
Thanks to everyone for getting back to me so quickly!!
Rose

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 03, 2006 1:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'nxs5@po.cwru.edu'; 'MCollins@peds.uab.edu'; 'AHensman@WIHRI.org'; 'scosby@peds.uab.edu'
Cc: 'kzaterka@rti.org'; 'Jon.E.Tyson@uth.tmc.edu'; 'Brenda.H.Morris@uth.tmc.edu'; 'Georgia.E.McDavid@uth.tmc.edu'; 'petrie@rti.org'; 'neil finer'
Subject: RE: oximeters

Alabama will send another 2 orange oximeters for a total of 4 orange.

We need two more orange - Can anyone provide these??
Thanks
Rose

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 03, 2006 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'nxs5@po.cwru.edu'; 'MCollins@peds.uab.edu'; 'AHensman@WIHRI.org'; 'scosby@peds.uab.edu'
Cc: 'kzaterka@rti.org'; 'Jon.E.Tyson@uth.tmc.edu'; 'Brenda.H.Morris@uth.tmc.edu'; 'Georgia.E.McDavid@uth.tmc.edu'; 'petrie@rti.org'; neil finer
Subject: RE: oximeters

Hi,
So far I have 1 Blue and 2 orange that Alabama will ship for arrival tomorrow.

Can anyone else help us??
Thanks
Rose

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 03, 2006 1:04 PM
To: 'nxs5@po.cwru.edu'; 'MCollins@peds.uab.edu'; 'AHensman@WIHRI.org'
Cc: 'kzaterka@rti.org'; 'Jon.E.Tyson@uth.tmc.edu';
'Brenda.H.Morris@uth.tmc.edu'; 'Georgia.E.McDavid@uth.tmc.edu';
'petrie@rti.org'
Subject: Fw: oximeters

Hi
Can any of you folks spare oximeters for UTHouston??
Let me know in the next hour if possible.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Mcdavid, Georgia E <Georgia.E.McDavid@uth.tmc.edu>
To: Morris, Brenda H <Brenda.H.Morris@uth.tmc.edu>; Tyson, Jon E
<Jon.E.Tyson@uth.tmc.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Oct 03 12:56:55 2006
Subject: FW: oximeters

From: Mcdavid, Georgia E
Sent: Tuesday, October 03, 2006 10:55 AM
To: 'Petrie, Carolyn'
Subject: oximeters

Carolyn,

We are in need of additional monitors for the SUPPORT study. Who do I need to contact? I need 1 blue monitor and 6 orange. We have (b) (6) [redacted] we just consented and twins. I have 2 orange and 7 blue monitors available at this time. Our other 9 monitors are in use.

Thanks,

Georgia

From: Neil Finer
To: Walsh, Michele; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; Wade Rich; Petrie, Carolyn
Cc: Auman, Jeanette O.; Pickett, James
Subject: RE: Suggested Support form revisions
Date: Tuesday, October 03, 2006 2:20:46 PM

Hi Michele
If everyone will review these, we can then discuss at the Steering Comm and come up with an overall approval or change as necessary.
Neil

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, October 03, 2006 10:15 AM
To: Zaterka-Baxter, Kristin; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; Wade Rich; Petrie, Carolyn
Cc: Auman, Jeanette O.; Pickett, James
Subject: RE: Suggested Support form revisions

Kristin:
Thanks for this grouping of proposed revisions.

All: Can we just discuss at the subcommittee meeting?
I am nervous about any minor changes that require IRB resubmissions
and/or software modifications.
Michele

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, September 28, 2006 1:33 PM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; Walsh, Michele; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; wrich@ucsd.edu; Petrie, Carolyn
Cc: Auman, Jeanette O.; Pickett, James
Subject: Suggested Support form revisions

Dear Support Subcommittee Members,

During the last Steering Committee meeting in July and on subsequent coordinator conference calls, several revisions were suggested for Support study forms Supp04, Supp05, Supp05A, Supp06, Supp08, and Supp12 (new). Over the last several months these revisions have been refined by a group of study coordinator with some comments and suggestions from Dr. Finer and Wade Rich. These drafts are attached for your review. We would like to discuss these suggestions during the upcoming Steering Committee meeting in October. Once discussions have concluded and if the committee finds the changes appropriate, the manual will be updated accordingly. Below please find a brief description of all changes and attached are copies of the draft forms with these changes highlighted.

Supp04:
1. It has been suggested that question **B.2** should be renumbered to subquestion B.1.**d.** Question B.2 *"Was a blood gas done within 30 minutes prior to intubation,* is only required to be answer if Q.B.1= yes *"Was the infant intubated for the first time within the first 14 days after admission to the NICU",* otherwise Q.B.2 is skipped, along with Q.B.1.a, b, and c. This revision has been drafted and would require reprogramming and a new forms version. An option would be to add a clarifying statement to Q.B.2;

"complete this question only if Q.B.1 = yes" which would require no DMS changes.

Supp05:

1. We've re-worked this form reformatting and renumbering to hopefully make it less confusing. All data points have remained the same with two exceptions; question 14 and 14a (about replacement oximeters) have been deleted because the new Supp12 will capture all oximeter replacement data, and the addition of code '9' (Mode of Support) to document "No support all day and off the study oximeter".

Supp05A

1. We've revised the instructions on this form to clarify its intended use as follows:
Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

2. We've deleted the Section B title "Intubated/Extubated Information (For NICU Only)" as this was a carry over from the old form and is no longer needed. This has prompted the subsequent renumbering of the form.

3. Previous Q.1.a (now Q.3.a) re. intubation has been revised removing the 'if yes' text and placing the text where it is now clear that both Q.3.a and 3.b must be answered if Q.3 = yes.

4. Based on discussions of relevant blood gas data in relation to intubation/extubation events, Dr. Finer has suggested that the pH, PCO2 should be reported if within 6 hours prior to the event (as stated currently on the Supp07 form). We've added question 'b.1', renumbered 'pH' and 'PCO2' to Q.b.1.a and Q.b.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

5. Previous Q.2.a (now Q.4.a) re. extubation has also been revised to by removing the 'if yes' text and placing the text where it is now clear that both Q.4.a and 4.b must be answered.

6. As in explanation #4 above, we've added question 'c.1', renumbered 'pH' and 'PCO2' to Q.c.1.a and Q.c.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

7. Previous Q.3 and 3a have been deleted because the new Supp12 will capture all oximeter replacement data

Supp06

Two types of protocol deviations have been added as options to select as listed below. We have also renumbered the 'Other' option to code '99' for ease of data programming:
Code 11. Incorrect randomization card select (incorrect gestational age group)
Code 12. Postnatal Steroids given for BPD/CLD within 21 days of life.

Supp08

Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting in July. The data that is intended to be captured are any AEs within the first 14 days of life only. The statement "*or prior to study status*" has been removed from the instructions on the form. Question 1 has been deleted and AE #1 (Air leak) has been revised by removing the statement "*in the first 14 days*"

New Supp12

This new form will capture all study oximeter replacement data throughout the study period from initiation to 36 weeks or status.

Your comments and suggestions are greatly appreciated.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

CELEBRATING 140 YEARS of Caring for Cleveland.

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu; Ronald N Goldberg; Ricki F Goldstein
Subject: Fw: SUPPORT MRI SECONDARY STUDY
Date: Tuesday, October 03, 2006 6:35:17 AM

Rose,

Also, please see Ricki's note below.

>
> How many patients have been enrolled in the Neuroimaging secondary
> at your site? **0**
>
> If your site has enrolled patients, has your site performed any
> study-related brain MRI's or cranial US yet? **N/A**

Kathy

Kathy J. Auten, MSHS
NICHD Neonatal Research Network Coordinator
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

----- Forwarded by Kathy J Auten/Pediatrics/mc/Duke on 10/03/2006 06:32 AM -----

Ricki F Goldstein <golds005@mc.duke.edu>

09/30/2006 01:00 PM

To Ronald N Goldberg <goldb008@mc.duke.edu>
cc auten002@mc.duke.edu, golds005@mc.duke.edu, Michael Cotten <cotte010@mc.duke.edu>
Subject Re: Fw: SUPPORT MRI SECONDARY STUDY

No one has been enrolled yet. The IRB has just been approved and there are 3 eligible infants to enroll in the nursery right now, none of whom are going home or being transferred anytime soon. One is in the TCN with an ostomy, and the other two are still sick in the ICN (babies XXX and YYY). We will approach the parents for consent when they are appropriate age.
Ricki

Ricki F. Goldstein MD
Associate Professor of Pediatrics
Director, High-Risk Infant Follow-up Program and
Special Infant Care Clinic
Division of Neonatology
Box 3179, Duke University Medical Center
Durham, NC 27710
office: 919-681-6024
pager: 919-970-(b)
fax: 919-681-4856

Ronald N Goldberg <goldb008@mc.duke.edu>
09/29/2006 05:04 PM

To
auten002@mc.duke.edu, golds005@mc.duke.edu, Michael Cotten <cotte010@mc.duke.edu>
cc

Subject
Fw: SUPPORT MRI SECONDARY STUDY

----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 09/29/2006 05:03 PM -----

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

To

09/29/2006 12:11 PM

cc
<susan.hintz@stanford.edu>

Subject
SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary by OCTOBER 3:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

(Embedded image moved to file: pic64914.gif)

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: Rebecca Bara
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: sshankar@med.wayne.edu
Subject: Re: FW: Wayne State SUPPORT call Tues, Oct. 3
Date: Monday, October 02, 2006 5:17:46 PM

Hi Rose,

No, we do not have screening logs for that secondary study as it is not yet IRB approved.

Becky

---- Original message ----
>Date: Mon, 2 Oct 2006 16:57:05 -0400
>From: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
>Subject: FW: Wayne State SUPPORT call Tues, Oct. 3
>To: "Shankaran, Seetha" <sshankar@med.wayne.edu>, <ae5357@wayne.edu>
>
> Seetha
>
> Or Becky
>
> Do you have any screening logs from the antenatal
> consent study? If so, can you send them to me?
> Thanks
>
> Rose
>
>
>
> ----------
>
> From: Petrie, Carolyn [mailto:petrie@rti.org]
> Sent: Monday, October 02, 2006 4:51 PM
> To: Petrie, Carolyn; Shankaran, Seetha; Becky;
> Higgins, Rosemary (NIH/NICHD) [E]; Bara, Rebecca
> (MED); Das, Abhik; Poole, W. Kenneth;
> nfiner@ucsd.edu; Wade Rich
> Cc: Townsend, Katrice; Zaterka-Baxter, Kristin;
> fmartinez@ucsd.edu; Webb, Robin E.
> Subject: RE: Wayne State SUPPORT call Tues, Oct. 3
>
>
>
> Reminder for tomorrow's call.
>
>
>
> ----------
>
> From: Petrie, Carolyn
> Sent: Friday, September 29, 2006 1:47 PM
> To: 'Shankaran, Seetha'; Becky;
> higginsr@mail.nih.gov; 'Bara, Rebecca (MED)'; Das,
> Abhik; Poole, W. Kenneth; 'nfiner@ucsd.edu'; 'Wade

> Rich'
> Cc: Townsend, Katrice; Zaterka-Baxter, Kristin;
> 'Fernando Martinez (fmartinez@ucsd.edu)'; Webb,
> Robin E.; Petrie, Carolyn
> Subject: Wayne State SUPPORT call Tues, Oct. 3
>
>
>
> The conference call to discuss the SUPPORT study is
> scheduled for
>
>
>
> Tuesday, October 3rd
>
> 1:00-1:45pm Pacific Time (4:00-4:45pm Eastern Time)
>
>
>
> To join the call,
>
> Dial Toll Free, 866-675(b) (6)
>
> Passcode: (b) (6)
>
>
>
> We would like to "brainstorm" with you and anyone at
> your site who obtains consent for SUPPORT. This can
> include faculty, fellows, research staff and
> others. We would like to assist in anyway to talk
> through recruitment at your site.
>
>

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Wayne State SUPPORT call Tues, Oct. 3
Date: Monday, October 02, 2006 4:54:36 PM

Rose,

We have good data on Yale, but very little for WS. Since they are not entering Ante data forms, could you request that they FAX us their handwritten log if they have one? It is better than nothing.
wade

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Monday, October 02, 2006 1:51 PM
To: Petrie, Carolyn; Shankaran, Seetha; Becky; higginsr@mail.nih.gov; Bara, Rebecca (MED); Das, Abhik; Poole, W. Kenneth; Neil Finer; Wade Rich
Cc: Townsend, Katrice; Zaterka-Baxter, Kristin; Fernando Martinez; Webb, Robin E.
Subject: RE: Wayne State SUPPORT call Tues, Oct. 3

Reminder for tomorrow's call.

From: Petrie, Carolyn
Sent: Friday, September 29, 2006 1:47 PM
To: 'Shankaran, Seetha'; Becky; higginsr@mail.nih.gov; 'Bara, Rebecca (MED)'; Das, Abhik; Poole, W. Kenneth; 'nfiner@ucsd.edu'; 'Wade Rich'
Cc: Townsend, Katrice; Zaterka-Baxter, Kristin; 'Fernando Martinez (fmartinez@ucsd.edu)'; Webb, Robin E.; Petrie, Carolyn
Subject: Wayne State SUPPORT call Tues, Oct. 3

The conference call to discuss the SUPPORT study is scheduled for

Tuesday, October 3rd
1:00-1:45pm Pacific Time (4:00-4:45pm Eastern Time)

To join the call,
Dial Toll Free, **866-675-**(b) (6)
Passcode: (b) (6)

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

From: Neil Finer
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Furey, Anne; Wade Rich
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Monday, October 02, 2006 1:47:52 PM

Hi Abhik
I understand – but we have advised the sites that when there is uncertainty because of clinical urgency etc that the procedure to follow is treat as a CPAP infant till the card can be pulled. The fact that the team worked to get the infant enrolled and then get the card in the face of an emergent clinical situation is quite impressive. I am concerned that making them complete a deviation is somewhat negative in the face of what was done. I understand the concern, but if the card is pulled early it also can unblind the team and may affect subsequent decisions. In this case the management was actually appropriate and per protocol. We designed this study to facilitate emergent care in just these situations.
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, October 02, 2006 10:37 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Furey, Anne; Wade Rich
Subject: RE: SUPPORT MRI SECONDARY STUDY

I think the deviation is not because of the treatment processes being followed (which worked out fine here), but because the randomization card was not pulled at the proper time.

Thanks

Abhik

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, October 02, 2006 1:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Furey, Anne; Das, Abhik; Wade Rich
Subject: RE: SUPPORT MRI SECONDARY STUDY

Hi Ivan and Rose
We have discussed this scenario and advised that the infant be treated as CPAP with intubation as necessary for resuscitation. If this infant was treated with positive pressure ventilation after delivery using PEEP, then the protocol was followed, albeit inadvertently. If this was done, I do not think that there was a protocol deviation. I do not see the need for a protocol deviation to be completed. Intubation for resuscitation is allowed for CPAP infants during resuscitation.

Here is the section of the protocol regarding CPAP infants in the DR:
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.
Hope this helps. This infant is your first enrollment.
Congratulations
Ivan you may want to discuss the approach for a consented infant for whom the randomization is not available with your team.
Be well

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 8:46 AM
To: Frantz, Ivan
Cc: Furey, Anne; Neil Finer; Adas@rti.org
Subject: RE: SUPPORT MRI SECONDARY STUDY

This sounds like the card was pulled late, but that the child would have been intubated for resuscitation anyway – this sounds like the infant can continue in the study and a "protocol deviation" is appropriate.

Thanks – hopefully the next one will be a little smoother. I hope the infant is doing well.

Rose

From: Frantz, Ivan [mailto:IFrantz@tufts-nemc.org]
Sent: Monday, October 02, 2006 11:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Furey, Anne; 'nfiner@ucsd.edu'
Subject: RE: SUPPORT MRI SECONDARY STUDY

It was tough as the delivery was a crash section for a prolapsed cord (b) (6) when I was out of town. The team didn't know what baby they were going in to resuscitate, and didn't realize it was a study baby until they were in the process of resuscitation. They then pulled the envelope and continued the resuscitation. As it turned out, the baby was assigned to CPAP, but required intubation for resuscitation. She was placed on the study oximeter, and CPAP guidelines followed. She is now extubated and on CPAP. I learned of all of this about 0200 today, and we are trying to sort out where we go from here. Technically I guess it is a protocol deviation, but did not have impact on the management of the infant. My hope is that we can proceed with the protocol, but need your input.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 11:29 AM
To: Frantz, Ivan
Cc: Furey, Anne; nfiner@ucsd.edu; susan.hintz@stanford.edu
Subject: RE: SUPPORT MRI SECONDARY STUDY

Ivan
This is great - any issues/questions with the first baby enrolled??
Thanks
Rose

From: Frantz, Ivan [mailto:IFrantz@tufts-nemc.org]
Sent: Monday, October 02, 2006 11:14 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Furey, Anne
Subject: RE: SUPPORT MRI SECONDARY STUDY

We have two consented patients, one of whom has delivered and started on the study, the other undelivered.

No studies performed.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 29, 2006 12:12 PM
Cc: susan.hintz@stanford.edu
Subject: SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary **by OCTOBER 3**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

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: Frantz, Ivan
To: "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Furey, Anne; nfiner@ucsd.edu; Gantz, Marie; Poole, W. Kenneth; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Monday, October 02, 2006 12:14:09 PM

What is the appropriate approach in the delivery room should a similar situation occur in the future? Pull the card late or not enroll the infant?

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, October 02, 2006 11:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Furey, Anne; nfiner@ucsd.edu; Gantz, Marie; Poole, W. Kenneth; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT MRI SECONDARY STUDY

Agreed.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 11:46 AM
To: Frantz, Ivan
Cc: Furey, Anne; nfiner@ucsd.edu; Das, Abhik
Subject: RE: SUPPORT MRI SECONDARY STUDY

This sounds like the card was pulled late, but that the child would have been intubated for resuscitation anyway - this sounds like the infant can continue in the study and a "protocol deviation" is appropriate.

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Sent: Monday, October 02, 2006 11:42 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Furey, Anne; 'nfiner@ucsd.edu'
Subject: RE: SUPPORT MRI SECONDARY STUDY

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 11:29 AM
To: Frantz, Ivan

Cc: Furey, Anne; nfiner@ucsd.edu; susan.hintz@stanford.edu
Subject: RE: SUPPORT MRI SECONDARY STUDY

Ivan
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Thanks
Rose

From: Frantz, Ivan [mailto:IFrantz@tufts-nemc.org]
Sent: Monday, October 02, 2006 11:14 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Furey, Anne
Subject: RE: SUPPORT MRI SECONDARY STUDY

We have two consented patients, one of whom has delivered and started on the study, the other undelivered.

No studies performed.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 29, 2006 12:12 PM
Cc: susan.hintz@stanford.edu
Subject: SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary **by OCTOBER 3**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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If you received this e-mail in error, please contact the sender and delete the e-mail and any attached material immediately. Thank you.

From: Susan Hintz
To: Furey, Anne
Cc: Higgins, Rosemary (NIH/NICHD) [E]; neil finer; IFrantz@tufts-nemc.org
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Monday, October 02, 2006 12:13:27 PM

Thanks so much Anne. This may be very helpful to others in the Network!

Susan

>I highlighted in yellow the corresponding text
>in both the ICF and the RAF as attached.
>
>-----Original Message-----
>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
>Sent: Monday, October 02, 2006 11:57 AM
>To: Furey, Anne; Susan Hintz; Frantz, Ivan
>Cc: neil finer
>Subject: RE: SUPPORT MRI SECONDARY STUDY
>
>
>Can you send us your exact language? This may be helpful for other
>sites who are having difficulty removing the PHI from the studies.
>
>Thanks
>Rose
>
>-----Original Message-----
>From: Furey, Anne [mailto:AFurey@tufts-nemc.org]
>Sent: Monday, October 02, 2006 11:55 AM
>To: 'Susan Hintz'; Frantz, Ivan
>Cc: Higgins, Rosemary (NIH/NICHD) [E]; Furey, Anne; neil finer
>Subject: RE: SUPPORT MRI SECONDARY STUDY
>
>
>We should not have any problems as we indicating in the consent form
>that PHI will be seen by study readers.
>
>> -----Original Message-----
>> From: Susan Hintz [mailto:srhintz@stanford.edu]
>> Sent: Monday, October 02, 2006 11:53 AM
>> To: IFrantz@tufts-nemc.org
>> Cc: higginsr@mail.nih.gov; AFurey@tufts-nemc.org; neil finer
>> Subject: RE: SUPPORT MRI SECONDARY STUDY
>>
>> << Message: Untitled Attachment >> << File: image001 18.gif >>
>>
>>
>**********
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>Attachment converted: Macintosh HD:SUPPORT ICF
>072806 C#5EDE50.doc (WDBN/«IC») (005EDE50)
>Attachment converted: Macintosh HD:NICHD NRN
>SUPPORT NE#5EDE51.doc (WDBN/«IC») (005EDE51)

From: Susan Hintz
To: Furey, Anne
Cc: neil finer; Higgins, Rosemary (NIH/NICHD) [E]; IFrantz@tufts-nemc.org
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Monday, October 02, 2006 12:03:15 PM

Perfect! That's what we did as well -

Thanks -

Susan

>We should not have any problems as we indicating in the consent form
>that PHI will be seen by study readers.
>
>> -----Original Message-----
>> From: Susan Hintz [mailto:srhintz@stanford.edu]
>> Sent: Monday, October 02, 2006 11:53 AM
>> To: IFrantz@tufts-nemc.org
>> Cc: higginsr@mail.nih.gov; AFurey@tufts-nemc.org; neil finer
>> Subject: RE: SUPPORT MRI SECONDARY STUDY
>>
>> << Message: Untitled Attachment >> << File: image001 18.gif >>
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>and delete the e-mail and any attached material immediately. Thank
>you.

--
Susan R. Hintz, M.D., M.S. Epi
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]; Mcdavid, Georgia E
Cc: Tyson, Jon E; Morris, Brenda H; srhintz@stanford.edu
Subject: RE: SUPPORT MRI SECONDARY STUDY
Date: Monday, October 02, 2006 11:36:38 AM

Awesome!!!
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 8:29 AM
To: Mcdavid, Georgia E
Cc: Tyson, Jon E; Morris, Brenda H; Neil Finer; srhintz@stanford.edu
Subject: RE: SUPPORT MRI SECONDARY STUDY

Terrific!!
Thanks for the update.

Rose

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Monday, October 02, 2006 11:19 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Tyson, Jon E; Morris, Brenda H
Subject: RE: SUPPORT MRI SECONDARY STUDY

Rose,
UT-Houston has enrolled 19 patients into the Neuroimaging secondary. 7 MRI and HUS have been performed, 2 infants have expired prior to the MRI/HUS being due, and all others are pending.
Georgia

From: Tyson, Jon E
Sent: Friday, September 29, 2006 4:13 PM
To: Mcdavid, Georgia E
Subject: FW: SUPPORT MRI SECONDARY 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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 29, 2006 11:12 AM
Cc: susan.hintz@stanford.edu
Subject: SUPPORT MRI SECONDARY STUDY

Please respond to the following questions pertaining to the SUPPORT Neuroimaging

secondary **by OCTOBER 3**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; Monica Collins
Subject: FW: 8 1 SUPPORT Recruitment Strategy Questionnaire
Date: Monday, October 02, 2006 9:39:02 AM
Attachments: 8 1 SUPPORT Recruitment Strategy Questionnaire.doc

---

Rose:

Monica and I did it together.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 02, 2006 8:15 AM
To: Wally Carlo, M.D.; Monica Collins
Cc: nfiner@ucsd.edu
Subject: 8 1 SUPPORT Recruitment Strategy Questionnaire

Wally and Monica
I can't find the answers that you folks submitted for this survey. We are trying to brainstorm with sites regarding modes of enhancing recruitment at sites. Your site does well at recruiting and the survey may help the network.

Thanks
Rose
<<8 1 SUPPORT Recruitment Strategy Questionnaire.doc>>

SUPPORT Recruitment Strategy Questionnaire

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment.

1. Please check all of the individuals who obtain SUPPORT consent at your site:
   1. Attending on-service Neonatologist _x____
   2. Neonatal fellow _x____
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator _x____
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) _x____
   7. Other – please describe

2. Who obtains consent at night and on the weekends at your site?
   1. Attending on-service Neonatologist _x____
   2. Neonatal fellow _x____
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator _x____
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) _x____
   7. Other – please describe _____
   8. No one currently available _____

3. List the provisions you have made at your site for recruitment at night and on the weekends:
   1. On call research staff __x___
   2. Clinical team obtains consent _x____ (can include attending, fellow, nurse practitioner)
   3. Other Research nurses come in routinely every day of the weekend to screen moms _____

4. How many sites were included for potential recruitment of patients at your study center? ___1____
   How many sites are actively recruiting patients at your study center? __1___
   If the answers to questions posed in #4 are not identical, please provide an explanation:

5. Does OB/Perinatology requests consults on a 24/7 basis on mothers who present with threatened preterm delivery at 23-27 weeks gestational age?
   _x__ yes
   ___ no

List items that have enhanced recruitment at your site:

The neo team checks the OB board at least twice a day
The research nurses check the OB board at least twice a day
We pay research nurses to come in during the weekend.
Research Nurses are full time employed
RNs have been educated in protocol

List items that have not helped recruitment that you anticipated would be helpful:

Consent many <28 w mom who are not likely to deliver

Please describe provisions you have made for this trial to insure recruitment 24 hours a day/7 days a week:

Ob notification to neonatology team upon admission of a < 28 w mom

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SURVEY 8.06.xls
Date: Saturday, September 30, 2006 11:34:11 AM

Thanks Rose
I didn't see Alabama on this survey. What's missing on these tables is the role of the PI! From yesterdays phone call it is somewhat concerning that the PI is involved in few of these interactions. That is the person who should be most committed, and who will encourage the others.
I believe that the PI needs to do more interaction with the Ob staff, and be more available to talk to Moms. As we heard this is a complicated study, and discussing this with an anxious family in an appropriate fashion is a challenge.
At a minimum the site PI for SUPPORT should do at least 1 consent per month with the Research coordinator and perhaps a fellow in tow.
I'll hold further judgment till the next calls.
I think these calls are helpful.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 29, 2006 11:15 AM
To: Neil Finer
Subject: SURVEY 8.06.xls

Neil
Here is the info from the survey

Rose
<<SURVEY 8.06.xls>>

From: M. Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: srhintz@stanford.edu; vanmeurs@leland.stanford.edu
Subject: Fwd: SUPPORT MRI SECONDARY STUDY
Date: Friday, September 29, 2006 6:17:07 PM

Hi Rose,
All 8 of our patients are enrolled in the Neuroimaging secondary.
We've done 4 study-related head ultrasounds. (On the other 4 patients: 1 missed, 1 died, 2 too early)
Best,
Beth

>>
>>
>>>X-Sieve: CMU Sieve 2.2
>>>Delivered-To: vanmeurs@stanford.edu
>>>Subject: SUPPORT MRI SECONDARY STUDY
>>>Date: Fri, 29 Sep 2006 12:11:36 -0400
>>>Thread-Topic: SUPPORT MRI SECONDARY STUDY
>>>Thread-Index: Acbj4fAL5zHOTF1iRBiuJzoDbMhKQg==
>>>From: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
>>>Cc: <susan.hintz@stanford.edu>
>>>
>>>Please respond to the following questions pertaining to the
>>>SUPPORT Neuroimaging secondary by OCTOBER 3:
>>>
>>>How many patients have been enrolled in the Neuroimaging secondary
>>>at your site?
>>>
>>>If your site has enrolled patients, has your site performed any
>>>study-related brain MRI's or cranial US yet?
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>>>
>>>
>>>
>>>
>>>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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>>><mailto:higginsr@mail.nih.gov>higginsr@mail.nih.gov
>>>
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>>>Content-Type: image/gif;
>>> name="image001.gif"
>>>Content-ID: <image001.gif@01C6E3C0.68F76EB0>
>>>Content-Description: image001.gif

>>>Content-Location: image001.gif
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>
>--
>Susan R. Hintz, M.D., M.S. Epi
>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

--
Bethany Ball
Neonatal and Developmental Medicine
Stanford University
750 Welch Road, Suite 315
Palo Alto, CA 94304

Tel (650) 725 8342
Fax (650) 725 8351

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer
Subject: Ante 01
Date: Friday, September 29, 2006 5:30:19 PM

Rose,

I think the data on the Ante 01 really brings everything regarding enrollment out in the open. If would be great if we could get that data for the SUPPORT phone conferences we have planned with Yale and Wayne St.

Wade

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]; ae5357@wayne.edu
Subject: RE: Wayne State SUPPORT call Tues, Oct. 3
Date: Friday, September 29, 2006 2:59:29 PM

Becky
Can we get Dawn to be on call---any other "committed" fellows too
Thanks
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 29, 2006 2:35 PM
To: Shankaran, Seetha; ae5357@wayne.edu
Subject: FW: Wayne State SUPPORT call Tues, Oct. 3

Seetha and Becky
It would be helpful if we had others who are involved in SUPPORT on the call.

Thanks
Rose

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, September 29, 2006 1:47 PM
To: Shankaran, Seetha; Becky; Higgins, Rosemary (NIH/NICHD) [E]; Bara, Rebecca (MED); Das, Abhik; Poole, W. Kenneth; nfiner@ucsd.edu; Wade Rich
Cc: Townsend, Katrice; Zaterka-Baxter, Kristin; fmartinez@ucsd.edu; Webb, Robin E.; Petrie, Carolyn
Subject: Wayne State SUPPORT call Tues, Oct. 3

The conference call to discuss the SUPPORT study is scheduled for

Tuesday, October 3rd
1:00-1:45pm Pacific Time (4:00-4:45pm Eastern Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

From: Susan Hintz
To: Brenda Poindexter
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT MRI SECONDARY
Date: Friday, September 29, 2006 2:31:29 PM

Brenda - thanks! Just remember that we want the study late cranial US and MRI within 7 days of each other. So, if you need to delay the MRI please also delay the CUS. Obviously, if you need a CUS for clinical reasons, that is another thing. But we would still need the "study" late CUS within 7 days of the MRI.

Thanks

Susan

> Absolutely...he should have a CUS anyway - and we'll keep the MRI in mind if he ever comes off the jet...
> Have a good weekend - Brenda
>
> On 9/29/06 1:55 PM, "Susan Hintz" <srhintz@stanford.edu> wrote:
>
> > Thanks for the reply. About the patient on the jet, you can definitely do the MRI and CUS later for those patients that cannot go to MRI at the "optimal" time due to clinical care issues. So, you could delay the MRI and late CUS to 42 weeks if needed - just a pitch to keep this patient on the potential list for the secondary!
> >
> > THanks
> >
> > Susan
> >
> > > We should have received approval on Wednesday (9/27); our only SUPPORT baby who is currently close to 36 weeks is still on the jet so he won't be able to go for a MRI yet.
> > > Brenda
> > >
> > > On 9/29/06 12:14 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
> > >
> > > Our last update from your

center was that SUPPORT Neuroimaging secondary was with your IRB or approval was pending minor modifications.

Please respond to the following **by October 3**:

Has your site received final IRB approval for the SUPPORT Neuroimaging secondary?

If yes, what was the approval date?

If IRB approval has been granted, how many patients has your site enrolled in the Neuroimaging secondary?

If your site has enrolled patients in the secondary, has your site performed any study-related brain MRI's or cranial US yet?

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: Susan Hintz
To: Angelita Hensman
Cc: Higgins, Rosemary (NIH/NICHD) [E]; kristin zaterka
Subject: Re: SUPPORT - Neuroimaging secondary
Date: Friday, September 29, 2006 1:56:23 PM

Thanks for the quick reply!

Susan

How many patients have been enrolled in the Neuroimaging secondary at your site? 9

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet? Yes.

8 have had study related CUS and MRI completed.

Angelita

--

Susan R. Hintz, M.D., M.S. Epi
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: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Abbot Laptook; Susan Hintz
Subject: SUPPORT - Neuroimaging secondary
Date: Friday, September 29, 2006 1:22:20 PM

How many patients have been enrolled in the Neuroimaging secondary at your site? 9

If your site has enrolled patients, has your site performed any study-related brain **MRI's or cranial US yet? Yes.**

8 have had study related CUS and MRI completed.

Angelita

From: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: susan.hintz@stanford.edu; Gaynelle Hensley; Pablo Sanchez; Walid Salhab
Subject: Re: SUPPORT MRI SECONDARY STUDY
Date: Friday, September 29, 2006 1:01:14 PM

Rose,
4 have been consented and all have had the MRI's and Cranial US's done.
Nancy

Nancy A. Miller, R.N.
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-502
Dallas, Texas 75390-9063
214-648-3780
pager 972-206-(b)

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 9/29/2006 11:11 AM >>>
Please respond to the following questions pertaining to the SUPPORT Neuroimaging secondary by OCTOBER 3:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

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: Petrie, Carolyn; mbball@stanford.edu; EKogut@LPCH.org; vanmeurs@stanford.edu; srhintz@stanford.edu; hclee@stanford.edu; nfiner@ucsd.edu; Das, Abhik; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Poole, W. Kenneth
Cc: Webb, Robin E.
Subject: RE: Stanford SUPPORT call, Fri Sept. 29 at 11am PT
Date: Friday, September 29, 2006 11:37:26 AM

Reminder for today's call.

Dear All-

The conference call to discuss the SUPPORT study is scheduled for

Friday, September 29th
11:00am-12:00pm Pacific Time (2:00-3:00pm Eastern Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

From: M. Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: nfiner@ucsd.edu; wrich@ucsd.edu; adas@rti.org; vanmeurs@stanford.edu; srhintz@stanford.edu; hclee@stanford.edu; EKogut@LPCH.org; kzaterka@rti.org; petrie@rti.org
Subject: SUPPORT enrollment call
Date: Thursday, September 28, 2006 7:50:53 PM
Attachments: Kathy_20060928_161545.pdf

To facilitate the discussion, a copy of the AP screening log covering 4/28 (date of IRB approval for re-start) to the present is attached.

MBB

Dear All-

The conference call to discuss the SUPPORT study is scheduled for

Friday, September 29th

11:00am-12:00pm Pacific Time (2:00-3:00pm Eastern Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)

Passcode: (b) (6)

We would like to "brainstorm" with you

and anyone at your site who obtains consent for SUPPORT. This can

include faculty, fellows, research staff and others. We would like

to assist in anyway to talk through recruitment at your site.

--

Bethany Ball
Neonatal and Developmental Medicine
Stanford University
750 Welch Road, Suite 315
Palo Alto, CA 94304

Tel (650) 725 8342
Fax (650) 725 8351

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Antenatal Screening and Consent
Screening Log

ANT01 Rel 1.0
October 5, 2005

Center: 15 Site (b) (6)

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 within the window >

Mother's Last Name	Mother's Hospital Number	Gestational Age (wks/days)	Last Date Eligible (Month/Day/Year)	Screening Number	Consent (Y/N)	**Pregnancy Outcome	Date of Birth (Month/Day/Year)	Enrolled In study Y/N	Network Number	Birth No.	
		27+2	(b) (6)	s001	Y	1	(b) (6)	Y	(b) (6)	1	✓
		25+2		s002	N	3				---	✓
		26+1		s003	N	2				---	✓
		26+2		s004	Y	1		Y		1	✓
		27+2		s005	N	1		N		1	✓
		27+0		s006	N	1		N		1	✓
		23+6		s007	N	1		N		1	✓
		26+3		s008	Y	3		clerk pass		---	✓
		26+4		s009	Y	1		Y		1	✓
		27+3		s010	Y	2		N		1	✓
		26+2		s011	N	1		N		1	✓
		27+4		s013	N	2				---	✓
		25+0		s012	N	1		N		1	✓
		23+5		s014	N	3		N		---	✓
		29+0		s015	Y	1		Y		1	✓
		27+4		s016	N	2		N		1	✓
		24 3		s017	Y [illegible]	3 [illegible]		N 69 bottles?		---	✓
		24 0		s018	N	4				---	✓
		27 3		s019	N	1		N		1	✓

**1 = Delivered in the window, 2= Delivered out of window, 3= Disc[illegible] weeks, 4= IUFD, 5= Stillborn

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
Antenatal Screening and Consent
Screening Log

ANT01 Rel 1.0
October 5, 2005

Center: 15 Site: (b) (6)

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 within the window >

Mother's Last Name	Mother's Hospital Number	Gestational Age (wks/days)	Last Date Eligible (Month/Day/Year)	Screening Number	Consent (Y/N)	**Pregnancy Outcome	Date of Birth (Month/Day/Year)	Enrolled in study Y/N	Network Number	Birth No.	
		27 4	(b) (6)	s 020	N	1	(b) (6)	N	(b) (6)	1	✓
		27 4		s 020	N	1		N		2	✓
		25 3		s 021	N Y	4 2				1	
		25 3		s 021	N Y	4 2				2	
		25 3		s 021	Y	4 2				3	
		24 3		s 022	N Y	1		Y		1	✓
		24 3		s 022	N Y	1		Y		2	✓
		26 5		s 023	N	1		N		1	✓
		26 5		s 024	Y	4				1	✓
		26 5		s 024	Y	4				2	✓
		24 1		s 025	N	1		N		1	✓
		24 6		s 026							
		25 6		s 027	Y						
		24 3		s 028							
		25 4		s 029	N	1		N		1	✓
		25 2		s 030	N	1		N		1	✓
				s							
				s							
				s							

**1 = Delivered in the window, 2= Delivered out of window, 3= Disch weeks, 4= IUFD, 5= Stillborn

From:	Zaterka-Baxter, Kristin
To:	nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@wihri.org; Walsh, Michele; wcarlo@peds.uab.edu; Roger Faix; bradley.yoder@hsc.utah.edu; Gantz, Marie; Nancy Newman; wrich@ucsd.edu; Petrie, Carolyn
Cc:	Auman, Jeanette O.; Pickett, James
Subject:	Suggested Support form revisions
Date:	Thursday, September 28, 2006 1:32:55 PM
Attachments:	SUPP04Admissionto NICU Form[08_31_06]uc.doc SUPP05SafetyMonitorRev08 31 06.doc SUPP05ASafetyMonitor[08.31.06](uc).doc SUPP06 Prot Dev[08.31.06](uc).doc SUPP08Adverse Event[08.31.06]Rev.doc SUPP12 oximeter replacement 08.31.06.doc

Dear Support Subcommittee Members,

During the last Steering Committee meeting in July and on subsequent coordinator conference calls, several revisions were suggested for Support study forms Supp04, Supp05, Supp05A, Supp06, Supp08, and Supp12 (new). Over the last several months these revisions have been refined by a group of study coordinator with some comments and suggestions from Dr. Finer and Wade Rich. These drafts are attached for your review. We would like to discuss these suggestions during the upcoming Steering Committee meeting in October. Once discussions have concluded and if the committee finds the changes appropriate, the manual will be updated accordingly. Below please find a brief description of all changes and attached are copies of the draft forms with these changes highlighted.

Supp04:

1. It has been suggested that question **B.2** should be renumbered to subquestion B.1.**d.** Question B.2 *"Was a blood gas done within 30 minutes prior to intubation,* is only required to be answer if Q.B.1= yes *"Was the infant intubated for the first time within the first 14 days after admission to the NICU",* otherwise Q.B.2 is skipped, along with Q.B.1.a, b, and c. This revision has been drafted and would require reprogramming and a new forms version. An option would be to add a clarifying statement to Q.B.2; *"complete this question only if Q.B.1 = yes"* which would require no DMS changes.

Supp05:

1. We've re-worked this form reformatting and renumbering to hopefully make it less confusing. All data points have remained the same with two exceptions; question 14 and 14a (about replacement oximeters) have been deleted because the new Supp12 will capture all oximeter replacement data, and the addition of code '9' (Mode of Support) to document "No support all day and off the study oximeter".

Supp05A

1. We've revised the instructions on this form to clarify its intended use as follows:
Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

2. We've deleted the Section B title "Intubated/Extubated Information (For NICU Only)" as this was a carry over from the old form and is no longer needed. This has prompted the subsequent renumbering of the form.

3. Previous Q.1.a (now Q.3.a) re. intubation has been revised removing the 'if yes' text and placing the text where it is now clear that both Q.3.a and 3.b must be answered if Q.3 = yes.

4. Based on discussions of relevant blood gas data in relation to intubation/extubation events, Dr. Finer has suggested that the pH, PCO2 should be reported if within 6 hours prior to the event (as stated currently on the Supp07 form). We've added question 'b.1', renumbered 'pH' and 'PCO2' to Q.b.1.a and Q.b.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

5. Previous Q.2.a (now Q.4.a) re. extubation has also been revised to by removing the 'if yes' text and placing the text where it is now clear that both Q.4.a and 4.b must be answered.

6. As in explanation #4 above, we've added question 'c.1', renumbered 'pH' and 'PCO2' to Q.c.1.a and Q.c.1.b to reflect this 6 hour window and have renumbered all subsequent questions accordingly.

7. Previous Q.3 and 3a have been deleted because the new Supp12 will capture all oximeter replacement data

Supp06

Two types of protocol deviations have been added as options to select as listed below. We have also renumbered the 'Other' option to code '99' for ease of data programming:

Code 11. Incorrect randomization card select (incorrect gestational age group)

Code 12. Postnatal Steroids given for BPD/CLD within 21 days of life.

Supp08

Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting in July. The data that is intended to be captured are any AEs within the first 14 days of life only. The statement "*or prior to study status*" has been removed from the instructions on the form. Question 1 has been deleted and AE #1 (Air leak) has been revised by removing the statement "*in the first 14 days*"

New Supp12

This new form will capture all study oximeter replacement data throughout the study period from initiation to 36 weeks or status.

Your comments and suggestions are greatly appreciated.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

DRAFT

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 ≥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_____

   d. Was a blood gas done within 30 minutes prior to intubation? Y N

   If Yes.

   1. Date: __/__/__ (Month Day Year) b. Time: __:__ (Hour Min)

   2. Source: ___

1= Arterial	2= Venous	3= Capillary

   3. pH ___

   4. pCO2 ___

   5. pO2 ___

   6. FiO2 ___

2. Was Surfactant given in the NICU? Y N

   If Yes,

a) Dose#	b) Date: (Month Day Year)	c) Time: (Hour Min)	d) Type:*
1	__/__/__	__:__	___
2	__/__/__	__:__	___
3	__/__/__	__:__	___
4	__/__/__	__:__	___

*1= Infasurf	2= Curosurf	3= Survanta	4= Exosurf	5= Other (Specify)

If Other (5), specify_____

Initials of person completing this form: ___

Complete a form each day through DOL 14 **1. Study Day:** __ __ **2. Date:** __ __ / __ __ / __ __ __ __.

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
2. 04 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
3. 06 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
4. 08 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
5. 10 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
6. 12 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
7. 14 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
8. 16 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
9. 18 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
10. 20 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
11. 22 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
12. 23 : 59	__ __ : __ __	__. __ __	___	__. __ __ __	___

5. Oximeter Alarm Checks Q6hr/day

a. __ __ : __ __

b. __ __ : __ __

c. __ __ : __ __

d. __ __ : __ __

6. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

4. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 08 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
2. 16 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
3. 23 : 59	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___

* Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

5-03387

NICU Network

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

DRAFT

SUPP05A version 3.0
Revised June 5, 2006
Revised August 31, 2006

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Report ~~This form should be completed~~ each time an intubation/extubation occurs after admission to the NICU through DOL 14. ~~in the same day.~~ Number each event sequentially.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N

If yes

a. Record the time of intubation __ __ : __ __ (Hr : Min)

b. Record the following prior to intubation :

1. Were blood gasses obtained within 6 hours prior to the event? If yes, Y N

a. pH __. __ __

b. PCO_2 __ __ __

2. FiO_2 __. __ __

3. Saturation __ __ __

4. Apnea? Y N

5. Sepsis/R/O Sepsis? Y N

6. Hemodynamic instability? Y N

7. Clinically significant PDA? Y N

8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N

If Yes,

a. If Yes, Record the time of extubation __ : __ __ (Min)

b. Type of extubation: __

1= Planned	2= Accidental

c. Record the following prior to extubation

1. Were blood gasses obtained within 6 hours prior to the event? If yes, Y N

a. pH __. __ __

b. PCO_2 __ __ __

2. FiO_2 __. __ __

3. Saturation __ __ __

Initials of person completing this form: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

3. Was the Infant intubated on this day? Y N

If yes

a. Record the time of intubation __ __ : __ __ (Hr : Min)

b. Record the following prior to intubation :

1. Were blood gasses obtained within 6 hours prior to the event? If yes, Y N

a. pH __. __ __

b. PCO_2 __ __ __

2. FiO_2 __. __ __

3. Saturation __ __ __

4. Apnea? Y N

5. Sepsis/R/O Sepsis? Y N

6. Hemodynamic instability? Y N

7. Clinically significant PDA? Y N

8. Other (specify)? _____ Y N

4. Was the Infant extubated on this day? Y N

If Yes,

a. If Yes, Record the time of extubation __ : __ __ (Min)

b. Type of extubation: __

1= Planned	2= Accidental

c. Record the following prior to extubation

1. Were blood gasses obtained within 6 hours prior to the event? If yes, Y N

a. pH __. __ __

b. PCO_2 __ __ __

2. FiO_2 __. __ __

3. Saturation __ __ __

Initials of person completing this form: __ __ __

PROTOCOL DEVIATION FORM

DRAFT

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)*~~

   11. Infant randomizes to incorrect gestational age group

   12. Postnatal steroids given for BPD/CLD within 21 days of life.

   99. 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: __ __ __

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: ___ ___ ___

The Surfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Replacement Oximeter Form

DRAFT

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

Complete this form each time a study oximeter is replaced from study initiation to 36 weeks or status.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
2.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
3.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
4.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
5.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
6.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
7.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
8.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
9.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___
10.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __ __	___

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: SUPPORT ROP DATA
Date: Thursday, September 28, 2006 9:16:15 AM

Thanks, Rose.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 28, 2006 8:58 AM
To: Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT ROP DATA

Here is some info from Alabama for ROP exams

Rose

From: Vivien Phillips [mailto:VPhillips@peds.uab.edu]
Sent: Wednesday, September 27, 2006 5:16 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins; Shirley Cosby
Subject: RE: SUPPORT ROP DATA

Please see response below. We're missing final ROP exam on 2 babies, waiting for results on one and attempting to call the primary care provider to inquire about eye exam.
Vivien

From: Wally Carlo, M.D.
Sent: Wednesday, September 20, 2006 9:41 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Monica Collins
Cc: Das, Abhik; Gantz, Marie; Vivien Phillips; Shirley Cosby
Subject: RE: SUPPORT ROP DATA

Rose: We will check it. wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 9:13 AM
To: Wally Carlo, M.D.; Monica Collins
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT ROP DATA

		No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
16	(b) (6)	There was no eye exam ever done on this baby prior to death.
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	Eyes matured, status reported
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	Eyes matured, status reported
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	Obtaining outpatient eye results and will enter results as soon as it's received
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	We're still tracking if follow up eye exam has been done. Loss contact with family at this time.
		50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	(b) (6)	Eyes matured, status reported
16	(b) (6)	SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
		Corrected SUPP09, yes to eye exam.

The above table shows missing ROP information needed for outcome for SUPPORT. Can you check to see if you have this information?

Thanks for all the hard work!!
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: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, September 27, 2006 4:19:48 PM

No, haven't heard from others, will reminde them

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 27, 2006 4:19 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT

Can you get this call set up??

-----Original Message-----
From: Rebecca Bara [mailto:ae5357@wayne.edu]
Sent: Tuesday, September 26, 2006 12:31 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: sshankar@med.wayne.edu; petrie@rti.org
Subject: SUPPORT

Hi Rose,

The data center has not received all the data regarding all the potentially eligible women I've screened/approached/consented/not delivered in the window, therefore what is in the monthly report is not the accurate total picture. Having said that, our enrollment remains at 4. Most weeks I'm in-house 6 days/week. We've recruited our fellows to join me in the study presentation/consent process on off-shifts with no additional consents to date. I would welcome any suggestions for success. A 2nd-year neonatal fellow Dawn Forbes, and I will be on a call that accomodates your, Seetha's and others' availability.

Thanks,
Becky

From: Petrie, Carolyn
To: nfiner@ucsd.edu; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; vineet.bhandari@yale.edu; harris.jacobs@yale.edu; monica.konstantino@yale.edu; richard.ehrenkranz@yale.edu; Poole, W. Kenneth; Zaterka-Baxter, Kristin
Cc: fmartinez@ucsd.edu; Petrie, Carolyn
Subject: Yale SUPPORT call
Date: Tuesday, September 26, 2006 4:02:21 PM

The conference call to discuss the SUPPORT study with Yale is scheduled for

Wednesday, October 4th
11:00am Eastern Time (8:00am Pacific Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

Please note that we wish to include both JoAnn Poulsen, RN and Janet Taft, RN but I do not have their email addresses (from the NRN website).

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

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: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: joint enrollment in MFM omega 3 trial and NRN SUPPORT trial
Date: Monday, September 25, 2006 7:27:15 PM

Rose, I have now reviewed the protocol for the MFM omega 3 fatty acid trial. For the following reasons it is my opinion that joint enrollment should be allowed:

Reasons why maternal participation in the MFM trial is undermine the SUPPORT trial or cause harm to the participating infants.

1) The rationale for the trial is to achieve a mean intake of omega 3 fatty acids that is like that some women consume from naturally occurring sources (fish) and achieve what may be referred to as "physiologic" blood or tissue levels--rather than "pharmacologic" levels—similar to that in populations with a low rate of preterm birth.
2) The best evidence that omega 3 fatty acid supplementation during pregnancy has an important effect is for preterm delivery. If omega 3 fatty acids truly result in a major reduction in preterm delivery, this would markedly diminish the likelihood that an infant whose mothers actually received omega three fatty acid supplements would end up in the SUPPORT trial, given the enrollment criteria for this trial. Moreover, 17 hydroxyprogesterone, an agent that has been shown to prevent preterm delivery, is administered to all women in the MFM trial. Finally, many of the mothers whose infants would be eligible for SUPPORT would have been ineligible for the MFM trial because they had not previously had a previous singleton preterm delivery, they had not received prenatal care between 16 and 22 weeks, or they refused informed consent. (As we discussed, only one infant in Houston in the SUPPORT trial was born to a mother in the MFM trial, and this mother may not have been in the intervention arm.) For this reason, the proportion of infants enrolled in SUPPORT who were born to mothers who received a generous intake of omega 3 fatty acids from naturally occurring sources may well be greater—perhaps substantially greater—than those born to mothers who received the active agent in the MFM trial
3) Based on what I read in the neonatal literature or in the MFM protocol or in the neonatal follow-up study (previously proposed from the Wake Forest group), there is little evidence to suggest direct or indirect harm to the infants and more reason to suspect benefit from delaying preterm delivery (even for infants enrolled in SUPPORT whose delivery might have been delayed from say 22 weeks to say 25 weeks) or from improved visual or cognitive development.
4) With randomization of infants in SUPPORT, it's likely that comparable numbers of infants born to mothers given omega 3 fatty acids would be enrolled in each treatment group. If so, omega 3 fatty acid supplementation would not cause confounding, whatever its effects on the infant.
5) If omega 3 fatty acid intake is found to be beneficial in the MFM trial, inclusion of the infants in the SUPPORT trial would, if anything, increase the generalizability of the results to the future when more of these women would be taking such an agent. If omega 3 fatty acid intake has no important effects, participation in the trial would have no effect on the generalizability of the results. The only problem would occur if omega 3 fatty acid intake would cause harm to infants in the trial. However, as noted above, this is unlikely and if we are sufficiently concerned about this possibility to proscribe participation in SUPPORT, we would also want to identify and proscribe participation of infants born to women with a high intake from fish or other sources outside the MFM trial.

Reasons why infant participation in the SUPPORT trial would not undermine the MFM Omega 3 Fatty Acid Trial

1) The SUPPORT trial could not affect the primary outcome in the MFM trial, in that this outcome (premature delivery) would occur prior to the infant's enrollment in the SUPPORT trial
2) As noted above few infants born to mothers in the MFM trial are likely to be enrolled in the SUPPORT Trial.
3) If anything, randomization of infants in the SUPPORT trial would reduce the background "noise and increase the signal to noise ratio due to variation in delivery room care and oxygen

saturation goals.

If this isn't clear, please let me know. If it is clear, feel free to share with other committee members or anyone else who has concerns about this issue.

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: Petrie, Carolyn
To: Petrie, Carolyn; mbball@stanford.edu; EKogut@LPCH.org; vanmeurs@stanford.edu; srhintz@stanford.edu; hclee@stanford.edu; nfiner@ucsd.edu; Das, Abhik; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Cc: Webb, Robin E.
Subject: Stanford SUPPORT call, Fri Sept. 29 at 11am PT
Date: Monday, September 25, 2006 3:27:25 PM

Dear All-

The conference call to discuss the SUPPORT study is scheduled for

Friday, September 29th
11:00am-12:00pm Pacific Time (2:00-3:00pm Eastern Time)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

We would like to "brainstorm" with you and anyone at your site who obtains consent for SUPPORT. This can include faculty, fellows, research staff and others. We would like to assist in anyway to talk through recruitment at your site.

From: Neil Finer
To: Petrie, Carolyn; Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Fernando Martinez
Subject: RE: SUPPORT
Date: Monday, September 25, 2006 2:58:00 PM

Lets try 11;00 - 12:00 AM
Neil

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Monday, September 25, 2006 10:43 AM
To: Neil Finer; Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Fernando Martinez; Petrie, Carolyn
Subject: RE: SUPPORT
Importance: High

Neil and Wade-

Currently the best time for the Stanford group is this Friday sometime between 10am-12pm Pacific Time.

Could you both be available either 10-11am or 11am-12pm PT??

Carolyn

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 21, 2006 4:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Cc: Wade Rich
Subject: RE: SUPPORT

Hi Rose
I will ask Wade to join any call that we arrange. Are we doing this next Monday? If so it would be better for me if the call was around 10:00 AM or after 2:00PM.
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 21, 2006 12:43 PM
To: petrie@rti.org
Cc: Neil Finer
Subject: Fw: SUPPORT

Can you set this up??
Also, neil - it may be productive for Wade to join this series of calls if he has time and availability - let us know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Krisa Van Meurs <vanmeurs@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Sep 21 16:39:14 2006
Subject: Re: SUPPORT

Rose,

We have actually been doing better with consents. Currently, we have at least a 1 set of (b) (6) consented, but they are approaching the end of their window so they may not add to our numbers of enrollees.

For the call, I would suggest:

Bethany Ball (mbball@stanford.edu)
Betsy Kogut (EKogut@LPCH.org)
Krisa Van Meurs (vanmeurs@stanford.edu)
Susan Hintz (srhintz@stanford.edu)
Henry Lee (hclee@stanford.edu)

I was unclear what date you wanted to do this. I am gone most of the day on 9-25 to take part in outreach at Salinas Hospital which is about 1.5-2 hours away.

Krisa

>Krisa
>We would like to set up a conference call to "brainstorm" with you
>and anyone at your site who obtains consent for SUPPORT. This can
>include faculty, fellows, research staff and others. We would like
>to assist in anyway to talk through recruitment at your site.
>Please provide a list of appropriate individuals for this call at
>you site by Monday (9/25). Neil, the data center, and I will join
>the call.
>
>Thanks
>Rose
>----------
>Sent from my BlackBerry Wireless Handheld

From: Fernando Martinez
To: Petrie, Carolyn; Neil Finer; Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, September 25, 2006 2:57:21 PM

Hi Carolyn,

I hope all is well. Dr. Finer and Wade can do 11am on Friday.

Thanks,
Fernando

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Monday, September 25, 2006 10:43 AM
To: Neil Finer; Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Fernando Martinez; Petrie, Carolyn
Subject: RE: SUPPORT
Importance: High

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Carolyn

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Sent: Thursday, September 21, 2006 4:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Cc: Wade Rich
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Neil

-----Original Message-----
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Sent: Thursday, September 21, 2006 12:43 PM
To: petrie@rti.org
Cc: Neil Finer
Subject: Fw: SUPPORT

Can you set this up??
Also, neil - it may be productive for Wade to join this series of calls

if he has time and availability - let us know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
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To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Sep 21 16:39:14 2006
Subject: Re: SUPPORT

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Betsy Kogut (EKogut@LPCH.org)
Krisa Van Meurs (vanmeurs@stanford.edu)
Susan Hintz (srhintz@stanford.edu)
Henry Lee (hclee@stanford.edu)

I was unclear what date you wanted to do this. I am gone most of the day on 9-25 to take part in outreach at Salinas Hospital which is about 1.5-2 hours away.

Krisa

>Krisa
>We would like to set up a conference call to "brainstorm" with you
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>include faculty, fellows, research staff and others. We would like
>to assist in anyway to talk through recruitment at your site.
>Please provide a list of appropriate individuals for this call at
>you site by Monday (9/25). Neil, the data center, and I will join
>the call.
>
>Thanks
>Rose
>---
>Sent from my BlackBerry Wireless Handheld

From: Neil Finer
To: Nancy Newman; Karen Osborne; nxs5@cwru.edu; kzaterka@rti.org; Wade Rich
Cc: Bradley Yoder; Roger Faix; Susan Tepper; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT form
Date: Monday, September 25, 2006 1:41:57 PM

Hi Karen and Nancy

I think that these are good questions. My principle concern for SUPPORT is to know whether an infant randomized to CPAP, requires intubation during resuscitation. This is allowed, and it may be difficult to determine this if the infant is in the NICU from 1 minute of age. We would need to distinguish an infant who requires intubation for resuscitation which usually occurs early, I would say almost always before 5 – 10 minutes of age from an infant who requires intubation later because of elevated PaCO2, apnea or elevated FiO2 etc. Our time in the DR study demonstrated that the average for the ELBW infant was 23 minutes, and almost all intubations are done < 10 minutes, the exceptions are those infants who required multiple attempts.

I think we can deal with this issue via documentation that resuscitation was complete at XX minutes, and perhaps record this for sites with NICU resuscitation.

Neil

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Monday, September 25, 2006 6:58 AM
To: 'Karen Osborne'; nxs5@cwru.edu; kzaterka@rti.org; Wade Rich
Cc: 'Bradley Yoder'; 'Roger Faix'; 'Susan Tepper'; higginsr@mail.nih.gov; Neil Finer
Subject: RE: SUPPORT form

Karen and group:

I was thinking more about the situation in Utah and I was concerned that using a 20 minute time could lead to mis-information if a resuscitation took much shorter OR more importantly much longer than 20 minutes and the infant was not responding to resuscitation efforts. Was there some way to identify for each infant when the resuscitation was complete (no matter what the length of time) – does the documentation start and continue on the same flow sheet or is there as separate resus. sheet for the initial care given??
Also, how would you record the surfactant given? Do you consider it administered in the Delivery room or NICU? And intubation?.....Just food for thought.....NN

From: Karen Osborne [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Friday, September 22, 2006 4:50 PM
To: nxs5@cwru.edu; kzaterka@rti.org; wrich@ucsd.edu
Cc: Bradley Yoder; Roger Faix; Susan Tepper; higginsr@mail.nih.gov; nfiner@ucsd.edu
Subject: RE: SUPPORT form

As most of you know, our babies are passed through a window from the labour and delivery OR as soon as they are born. Therefore, SUPP03 and SUPP04 will both use the arbitrary 20 minute time frame as the delivery time and admission time are the same at our facility. Our source docs will definitely support the

data on SUPP04 as the baby is resuscitated in the NICU. There is no transition area prior to admission to the NICU. Per Wade's comment, we would not of course, document an incorrect admission time.
We will use the first sat and FiO2 that is recorded for questions A, 3 and 4 as suggested. However, this doesn't resolve question A, 2 which is; "Respiratory support on admission to the NICU". We have the option of entering '7' no support and perhaps this is what we should do.
After talking with Nancy Newman, it appears that the other issue is, the data base will throw out a query if the time of delivery and time of admission to the NICU are the same, which in our case they will be. For our data forms to match our source documents they have to remain the same. The options as I see them are to 1) we write a comment for every baby enrolled to override the query, 2) have the data base programmed to accept the birth and admission time as being the same.

I'd appreciate any and all input on what we should do with these two data issues. I realize they are not crucial to the outcomes of the study, but we do need to get them sorted so we can complete the data as required.

Thank you!

Karen

>>> "Wade Rich" <wrich@ucsd.edu> 11:37 AM 9/22/200622/2006 >>>
Karen,
We gave you an arbitrary time relative to the SUPP03 in order to differentiate resuscitation events from those which occur later. (i.e. was the infant intubated for resuscitation, or was he stabilized and intubated later). I do not think it makes sense to continue this on SUPP 04, as your source documents will not support the data. Your admission time is your admission time. The first sat available to you after that time should be your admission saturation, and ditto the FiO2. It is OK to define an arbitrary time as "the resuscitation window", but it is not OK to document an incorrect admission time.
I am cc'ing Neil with this, but I am fairly certain he agrees.
Wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, September 22, 2006 10:21 AM
To: Nancy Newman
Cc: Wade Rich
Subject: FW: SUPPORT form

Hi,

Please see the question below from Karen Osborne at Utah regarding Supp04 Q.A2 - 4 and resuscitation in the NICU as opposed to L&D. Please cc me on the answers so I can tuck it away JIC.

Thanks,

Kris

From: Karen Osborne [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Tuesday, September 19, 2006 7:30 PM
To: Zaterka-Baxter, Kristin
Subject: SUPPORT form

Hi Kris,

I have a question for you on the 'Admission and Procedures' SUPPORT form;

Section A, question 2, 3 and 4 are very specific to those centers that resuscitate their babies in labor and delivery. As we resuscitate our babies in the NICU, these questions don't seem to apply to our center. Do we use the 20 minute rule for these questions and if so, at what point do we collect the data for the sat and FiO2 during that 20 minutes? We are fine with the rest of the form, it's just these 3 questions that we aren't sure what data we should use to complete them.

Thanks!

Karen

From: Neil Finer
To: Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT form
Date: Monday, September 25, 2006 9:41:46 AM

FYI
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Monday, September 25, 2006 6:34 AM
To: Neil Finer
Subject: RE: SUPPORT form

neil,
We don't currently but we wiill determine a predefined length of time for "resuscitation". We have loosely been going with about 15 minutes, but I think we need to calrify that for all our staff.
Thanks.

Brad

Bradley A. Yoder, MD
Professor of Pediatrics
University of Utah School of Medicine
Dept of Pediatrics/Neonatology
PO Box 581289
Salt Lake City, UT 84158-1289

Phone: 801-581-7052
Pager: 801-339(b) (6)
FAX: 801-585-7395
Email: bradley.yoder@hsc.utah.edu

For courier delivered mail, the physical address is:

Williams Building
295 Chipeta Way, Room 2N114
Slat Lake City, UT 84108
>>> "Neil Finer" <nfiner@ucsd.edu> 09/23/06 7:00 PM >>>

Hi Brad
I think that noting the admit time is one minute later than birth is OK - in reality its probably 20-30 seconds
We also want to know the resuscitation interventions and so at Salt Lake we need to know what you consider the duration of resuscitation. Do your nursing/physician notes define the end of resuscitation interventions? If an infant is placed on CPAP at 1 minute but required intubation at 10 minutes will that be considered a resuscitation intervention? Now if this is a CPAP infant in SUPPORT, this would allowed by protocol - however it this was considered to occur in the NICU, you would have to document the indication for intubation to ensure that you are following protocol. Can you think about this and let us know how you would define the end of resuscitation interventions. For a control infant, this is

not an issue as you have an hour to give the surf, and you could start CPAP and then intubate at 59 minutes and give surf and still be following protocol.
Thanks for considering this.
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Saturday, September 23, 2006 8:06 AM
To: nxs5@cwru.edu; Karen Osborne; kzaterka@rti.org; Wade Rich
Cc: Roger Faix; Susan Tepper; higginsr@mail.nih.gov; Neil Finer
Subject: RE: SUPPORT form

Regardng the time of birth and time of admission....can we not, as a standard, just make them 1 minute different? Example, TOB = 14:40 and TOA = 14:41. In point of fact the exact time of admission is not the same as the time of birth, and we can make the assumption that it takes at least 30 seconds to get the cord cut & clapmed & the baby transferred thru the window....so we round it up to a minute.

Regarding respiratory support at time of admission. They are in fact on no support, so we should record it as such.

BAY

>>> Karen Osborne 09/22/06 2:49 PM >>>
As most of you know, our babies are passed through a window from the labour and delivery OR as soon as they are born. Therefore, SUPP03 and SUPP04 will both use the arbitrary 20 minute time frame as the delivery time and admission time are the same at our facility. Our source docs will definitely support the data on SUPP04 as the baby is resuscitated in the NICU. There is no transition area prior to admission to the NICU. Per Wade's comment, we would not of course, document an incorrect admission time.
We will use the first sat and FiO2 that is recorded for questions A, 3 and 4 as suggested. However, this doesn't resolve question A, 2 which is; "Respiratory support on admission to the NICU". We have the option of entering '7' no support and perhaps this is what we should do.
After talking with Nancy Newman, it appears that the other issue is, the data base will throw out a query if the time of delivery and time of admission to the NICU are the same, which in our case they will be. For our data forms to match our source documents they have to remain the same. The options as I see them are to 1) we write a comment for every baby enrolled to override the query, 2) have the data base programmed to accept the birth and admission time as being the same.

I'd appreciate any and all input on what we should do with these two data issues. I realize they are not crucial to the outcomes of the study, but we do need to get them sorted so we can complete the data as required.

Thank you!

Karen

>>> "Wade Rich" <wrich@ucsd.edu> 11:37 AM 9/22/200622/2006 >>>

Karen,

We gave you an arbitrary time relative to the SUPP03 in order to differentiate resuscitation events from those which occur later. (i.e. was the infant intubated for resuscitation, or was he stabilized and intubated later). I do not think it makes sense to continue this on SUPP 04, as your source documents will not support the data. Your admission time is your admission time. The first sat available to you after that time should be your admission saturation, and ditto the FiO2.

It is OK to define an arbitrary time as "the resuscitation window", but it is not OK to document an incorrect admission time.

I am cc'ing Neil with this, but I am fairly certain he agrees.

Wade

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, September 22, 2006 10:21 AM
To: Nancy Newman
Cc: Wade Rich
Subject: FW: SUPPORT form

Hi,Please see the question below from Karen Osborne at Utah regarding Supp04 Q.A2 - 4 and resuscitation in the NICU as opposed to L&D. Please cc me on the answers so I can tuck it away JIC.Thanks,Kris

From: Karen Osborne [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Tuesday, September 19, 2006 7:30 PM
To: Zaterka-Baxter, Kristin
Subject: SUPPORT form

Hi Kris,

I have a question for you on the 'Admission and Procedures' SUPPORT form;

Section A, question 2, 3 and 4 are very specific to those centers that resuscitate their babies in labor and delivery. As we resuscitate our babies in the NICU, these questions don't seem to apply to our center. Do we use the 20 minute rule for these questions and if so, at what point do we collect the data for the sat and FiO2 during that 20 minutes? We are fine with the rest of the form, it's just these 3 questions that we aren't sure what data we should use to complete them.

Thanks!

Karen

From: Neil Finer
To: Gantz, Marie
Cc: Das, Abhik; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Friday, September 22, 2006 6:09:56 PM

Thanks Marie.
As expected the >96% is greater - 18% vs 10% after 14 days as is the < 84% 12% vs 8%.
Hopefully the sites will now concentrate on these infants to maintain better SpO2 control. This data will serve as a baseline moving forward.
Thanks for this.
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 22, 2006 2:44 PM
To: Neil Finer
Cc: Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data for the SUPPORT Trial

Hi Neil,

The oximeter reports have just been sent to the centers. Here is the overall report, with oximeter processed through today.

Have a great 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

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 19, 2006 8:30 PM
To: Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; Das, Abhik; Gantz, Marie; Poole, W. Kenneth; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
We have a brief call to discuss SUPPORT planned for Thursday. I would like to discuss the following with you:
1. Recruitments
2. The format of Oximeter data to send to the sites (See attachment as

an Example)
3. Other issues
Please let me know if you want to add items to this agenda.
Thanks
Neil

Blansfield, Earl (NIH/NICHD) [E]

From: Walsh, Michele <Michele.Walsh@uhhs.com>
Sent: Thursday, September 21, 2006 1:30 PM
To: Higgins_Rosemary_; Neil_Finer
Subject: SUPPORT enrollment

Hi:
I just wanted to raise off line-
the issue.that this lagging enrollment at Wayne State and Yale is not new. If you look at the other RCTs both have been low enrollers- unless they were the PI.
Michele

From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; kurt.schibler@cchmc.org; alaptook@WIHRI.org; mcw3@cwru.edu; wcarlo@peds.uab.edu; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Bradley.Yoder@hsc.utah.edu; Gantz, Marie; nxs5@cwru.edu; wrich@ucsd.edu; Petrie, Carolyn; Zaterka-Baxter, Kristin
Cc: KaFallon@peds.uab.edu; msumner@peds.uab.edu; "fmartinez@ucsd.edu
Subject: FW: Call for Oximeter data for the SUPPORT Trial
Date: Thursday, September 21, 2006 8:54:49 AM

Just a reminder that the call to discuss the Oximeter data for the SUPPORT Trial is scheduled for today:

Thursday, September 21
1:00pm ET

Dial:
Outside the USA
1-203-310(b) (6)

or
Within the USA
866-675(b) (6)

Then, enter Participant Passcode:
(b) (6)

Please let me know if you have any questions.

Thanks,
Robin

From:	Neil Finer
To:	Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Wednesday, September 20, 2006 8:31:35 PM
Attachments:	SUPPORT Enrollment 9-20-06.doc

Hi Everyone
Marie, God bless her, produced these enrollment estimates.
Let's briefly discuss tomorrow
Thanks Marie
Neil

-----Original Message-----
From: Neil Finer
Sent: Tuesday, September 19, 2006 4:30 PM
To: 'Bradley Yoder'; 'mcw3@case.edu'; 'nxs5@case.edu'; 'kurt.schibler@cchmc.org'; 'Roger Faix'; 'higginsr@mail.nih.gov'; 'WCarlo@peds.uab.edu'; 'adas@rti.org'; 'mgantz@rti.org'; 'poo@rti.org'; 'ALaptook@wihri.org'
Cc: 'higginsr@mail.nih.gov'; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
We have a brief call to discuss SUPPORT planned for Thursday. I would like to discuss the following with you:
1. Recruitments
2. The format of Oximeter data to send to the sites (See attachment as an Example)
3. Other issues
Please let me know if you want to add items to this agenda.
Thanks
Neil

SUPPORT Enrollment as of September 20, 2006

Total Enrolled

Time period	Enrolled
Through Nov05	249
Mar06-Sep06	134
Total	383

Enrollment by Center March 2006 – September 2006

Center	Mar-06	Apr-06	May-06	Jun-06	Jul-06	Aug-06	Sep-06	Total
3	5	6	4	2	1	3	1	22
4	0	1	1	3	0	3	0	8
5	2	1	0	1	0	0	0	4
9	0	3	2	4	2	1	0	12
11	0	0	0	1	1	7	2	11
12	0	0	4	2	1	0	2	9
13	0	0	1	1	0	1	0	3
14	0	2	2	7	3	0	4	18
15	0	1	1	0	2	0	0	4
16	0	0	0	6	6	7	0	19
18	0	5	1	3	1	5	0	15
19	0	0	1	3	3	1	0	8
21	1	0	0	0	0	0	0	1
Total	8	19	17	33	20	28	9	134
# Enrolling	3	7	9	11	9	8	4	
Avg/center	2.7	2.7	1.9	3.0	2.2	3.5	2.3	

Average Enrollment Per Center Per Month

Time period	Total enrolled	Average # of centers enrolling	Average per center per month
Apr06-Aug06	117	8.8	2.7
Jun06-Aug06	81	9.3	2.9

Months Needed to Enroll Remaining 927 Patients

Average per center per month	Number of centers enrolling								
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
2	58	52	47	43	39	36	34	31	29
2.5	47	42	38	34	31	29	27	25	24
3	39	35	31	29	26	24	23	21	20

From: CATHY A. GRISBY
To: Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org
Cc: Das, Abhik; Gantz, Marie
Subject: Re: SUPPORT ROP DATA
Date: Wednesday, September 20, 2006 2:34:43 PM

Lenora addressed these a few months ago. She spoke with Scott for help. She will be contacting RTI again to see where the glitch is. I'll keep you posted.

Cathy

---- Original message ----

Date: Wed, 20 Sep 2006 10:10:04 -0400
From: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
Subject: SUPPORT ROP DATA
To: <kurt.schibler@cchmc.org>, <grisbyca@email.uc.edu>
Cc: "Das, Abhik" <adas@rti.org>, "Gantz, Marie" <mgantz@rti.org>

11	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

11	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	(b) (6)	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.

The above table shows missing ROP information needed for outcome for SUPPORT. Can you check to see if you have this information?

Thanks for all the hard work!!

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Gantz, Marie
To: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Cc: Das, Abhik
Subject: RE: SUPPORT ROP DATA
Date: Wednesday, September 20, 2006 1:22:32 PM

Thanks, Wade. We do have the data on [redacted] – we just received it after the missing forms report was generated this month. For [redacted] though, the infant had not reached ROP final status as defined by the SUPPORT MOP at the time of the last exam (3/30/06). The lowest zone of any vessels in each eye was 3, but we need the lowest zone to be 3 for two exams in a row to say that the infant has no ROP.

Marie

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mgantz@rti.org

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, September 20, 2006 12:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT ROP DATA

[redacted] is lost to everything. They are in another country, and owe us a lot of money...
[redacted] are completed.
[redacted] are pending.

Wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 7:18 AM
To: Neil Finer; Wade Rich
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT ROP DATA

22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

The above table shows missing ROP information needed for outcome for SUPPORT. Can you check to see if you have this information?

Thanks for all the hard work!!
Rose

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Wade Rich
To: Maribeth Sayre; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kristin Zaterka-Baxter (E-mail); Chris Novak; Vicki Bishop; George Yaghnam
Subject: RE: NICHD NRN Support Study Masimo oximeters
Date: Wednesday, September 20, 2006 12:55:16 PM

I checked one. They are in fact skewed.
Wade

From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Wednesday, September 20, 2006 9:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kristin Zaterka-Baxter (E-mail); Wade Rich; Chris Novak; Vicki Bishop; George Yaghnam
Subject: RE: NICHD NRN Support Study Masimo oximeters

Hi Rose,

According to our records, they were masked.
The easiest way to check is with a simulator set at 90%.
They can be checked at UAB, or sent back to Irvine for checking and changing to the SUPPORT histogram.
To send them back, please follow the procedure outlined beow.
I am again attaching the RMA form.

Maribeth

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 9:09 AM
To: Maribeth Sayre
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: NICHD NRN Support Study Masimo oximeters

HI,
Can you let us know if these were correctly blinded?
Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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higginsr@mail.nih.gov

From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Tuesday, September 19, 2006 1:41 PM
To: Zaterka-Baxter, Kristin; Chris Novak; Vicki Bishop; George Yaghnam
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD NRN Support Study Masimo oximeters

Hi Kristin,

The easiest way to test the oximeters is to set the simulator at 90%.
The oximeter should read either 93 or 87.
I don't know why these oximeters have the standard histogram instead of the SUPPORT histogram.
The good news is that our process has changed, so this should not be a problem in the future.
To change the histograms, please send the oximeters back to Irvine. You will need to call for a RMA#,
fill out the attached form noting that these are masked oximeters that need to have the histogram changed to the SUPPORT histogram, and send to the attention of Chris Novak.
Masimo will pay the shipping charges.

Thanks,
Maribeth

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, September 18, 2006 10:37 AM
To: Maribeth Sayre; Chris Novak; Vicki Bishop
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: NICHD NRN Support Study Masimo oximeters

Hi Marybeth,

Please find below masimo oximeter serial numbers of instruments found recently to have seemingly normal histogram ranges instead of the skewed ranges required for the masked NRN Support study. These are not new oximeters but instead have been recently moved from our Miami site to the University of Alabama site where the histogram ranges were notice to be different than what was viewed on their current oximeters of the same color code. We're not sure if this has affected the data in any way or if it's something that's possibly just incorrect on the visual screen. We are in the process of trying to test one of these oximeters with an oximeter simulator but this will not take place until tomorrow at the earliest.

These are the oximeters that were originally sent to the University of Miami on April 7, 2005.

317219
317312
317363
317393
317408
317420
317431
317443

These are the histogram ranges on the Miami Masimo's and our UCSD study coordinator has told me these are also the standard for Masimo's off the shelf.

96-100%
91-95%
86-90%
81-85%
<85%

Please let me know if you need further information to look into this matter; I'd be happy to send you whatever is needed.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich; Vineet
Subject: Re: FW:
Date: Wednesday, September 20, 2006 12:49:03 PM

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> See note – still need to have a FU exam.
>
> Thanks
> Rose
>
> **From:** Gantz, Marie [mailto:mgantz@rti.org]
> **Sent:** Wednesday, September 20, 2006 12:19 PM
> **To:** Higgins, Rosemary (NIH/NICHD) [E]
> **Cc:** Das, Abhik
> **Subject:** RE:
>
> We do have three exams for that infant, entered by the center on 8/30/06. However, the infant had not met ROP acute/final status as defined by the SUPPORT MOP. The lowest zone of any vessels in both eyes was still 2=II, and the highest stage ROP in any zone was 2=Stage 2.
>
> 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:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Wednesday, September 20, 2006 12:10 PM
To: Gantz, Marie
Cc: Das, Abhik
Subject: FW:

See below – entered on August 30 – perhaps a problem with transmission??
Thanks

Rose

From: Monica Konstantino [mailto:monica.konstantino@yale.edu]
Sent: Wednesday, September 20, 2006 12:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich; Vineet
Subject: Re:

Higgins, Rosemary (NIH/NICHD) [E] wrote:

13	50 weeks PMA has been reached and final ROP exam status has not (b) (6) been reported on the SUPP10 for either eye.

The above table shows missing ROP information needed for outcome for SUPPORT. Can you check to see if you have this information?

Thanks for all the hard work!!
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

We were able to get the final ROPexams for baby (b) (6) It was entered on August 30- we double checked to make sure it was entered. Perhaps the data was not transmitted before the Sept report. thanks,
Monica

We checked the SUPP10 form and the first 3 exams were entered on August 30 of last year, the other 6 exams we entered on August 31 of this year. The baby had a total of 9 exam that we have results for, 4 of these were done as an outpatient. Let me know if there is anything else you need.
Monica

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT AE
Date: Wednesday, September 20, 2006 10:54:31 AM

Hi Rose,

Kris looked at the Medwatch forms and found no reported esophageal perforations. Below I have listed (verbatim) the "other" adverse events listed on the SUPP08. Assuming that "spont. perf" refers to intestinal perforation, no esophageal perforations have been entered.

ino 6/29
cpr 0624
NEC epi req. drain, then surgery
spontaneous gi perforation
early onset sepsis-e.coli
Spontaneous perforation of bowel-drain placed
Pheumothorax requiring chest tube intervention
PIE in L lung
Sepsis e-coli
Intest perforation
enal failure-oliguria
abdominal perforation
spont. perf
NEED FOR VOLUME IN DR/DONOR TWIN T2T
pneumoperitoneum
severe bradcardia episodes
CPR and Epi given x2 for cardiac arrest
nasal bruising
skin breakdown at the middle columella of nose
sm. skin breakdown noted on nares (base of septum)

Marie

Marie Gantz, Ph.D.
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RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 9:01 AM
To: Das, Abhik; Zaterka-Baxter, Kristin
Cc: Gantz, Marie
Subject: SUPPORT AE

Hi,
I got a SUPPORT AE from Utah (clinical site (b) (6) network number (b) (6) for a child who had an esophageal perforation – have we had any other esophageal perforations??
Thanks
Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network
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From:	Wally Carlo, M.D.
To:	Gantz, Marie; Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; ALaptook@wihri.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Wednesday, September 20, 2006 10:41:00 AM

It may be best to separate to be able to discern the saturations in the two periods best. wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 20, 2006 9:19 AM
To: Wally Carlo, M.D.; Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; Das, Abhik; Poole, W. Kenneth; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

In answer to Wally's question, "through 36 weeks" includes days 1-14.

Marie

Marie Gantz, Ph.D.
Research Statistician
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P.O. Box 12194
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mgantz@rti.org

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 20, 2006 8:04 AM
To: Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; Das, Abhik; Gantz, Marie; Poole, W. Kenneth; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Neil:

Looks great! Does the "through 36 weeks" exclude 1-14 days?

Something else to consider is whether there should be some monitoring of

the separation of the ventilation arm. The easiest to monitor may be PCO2s or vent days. This would be only for the first 14 days. The range of separation in previous trials is 4-7 torr on the CO2.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 19, 2006 7:30 PM
To: Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
We have a brief call to discuss SUPPORT planned for Thursday. I would like to discuss the following with you:
1. Recruitments
2. The format of Oximeter data to send to the sites (See attachment as an Example) 3. Other issues Please let me know if you want to add items to this agenda.
Thanks
Neil

From: Das, Abhik
To: Neil Finer
Cc: Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Gantz, Marie
Subject: RE: BPD definition for SUPPORT
Date: Wednesday, September 20, 2006 10:40:42 AM

Neil:

Sorry for the delayed response. With regard to your point 3 about two possible diagnoses for BPD, I understand your point; but for the purposes of determining efficacy in this randomized controlled trial, we do need one single definition for the primary outcome, before viewing the data (for interim DSMC analyses and for the primary analysis after the study ends). Secondary analyses using other definitions of BPD are fine. Since the protocol states that physiologic definition of BPD would be used, I think we should stick to that for the primary outcome. The complication is for cases where the physiologic definition is not available. In that case, as in the Benchmarking trial, we should perhaps revert to the old GDB definition of BPD. (By the way, in answer to your question in 6, under the old definition, infants on CPAP or vents at 36 weeks were **not** called BPD if they were not in oxygen.) An additional complication here is that GDB forms have changed midstream through SUPPORT; so we would have to account for that.

As for discharged and transferred patients (#5), if they were discharged or transferred before 36 weeks, we still need a primary outcome determination on them, so it seems to me that we still need to use whether they were on oxygen when transferred or discharged (except for those transferred patients for whom we have data from the recieving hospital) to determine BPD.

In order to accommodate all these complexities in our data structure, we thus have the very complicated and scary looking algorithm that Marie sent out earlier. We need to revise it with your input and finalize the definitions in time for us to be able to do the first interim look at the data when the necessary numbers are accrued. I leave it to you to decide whether this is something you want to bring up at tomorrow's call or get off-line input from Michele (or anybody else) on.

Thanks

Abhik

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 14, 2006 7:02 PM
To: Gantz, Marie
Cc: Das, Abhik; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: BPD definition for SUPPORT

Hi Marie
SUPPORT can use the following for the definition of BPD

1. NG07 which indicates that the infant is on Oxygen at 36 weeks which we should use for the primary hypothesis
2. For infants who have had the Physiologic Challenge, we should record the results as per form PHY 01 or 02 to indicate that the infant has BPD by this criteria
3. For any infant therefore, we can have 2 possible diagnoses of BPD, the need for Oxygen and the result of physiologic challenge. We will analyze using both of these, although the numbers will not be identical, in either numerator or denominator
4. The flow diagram would be much simpler if there was a top row indicating infants who are not requiring oxygen or any form of support as a separate category. This will the largest category
5. We can then describe infant who are transferred/discharged and infants who are on oxygen and /

or any form of support. All transferred infants are presumably not challenged – the exceptions are transfers to another Network Center

6. I would then simplify this by having a column of infants who are on CPAP/Mechanical Ventilator – these are all categorized as having BPD irrespective of their FiO2 (Abhik and Ken – in the past before the physiologic challenge, were infants on CPAP or vents at 36 weeks called BPD if they were not in oxygen??)

This now allows only one column that needs expansion/explanation – those infants on oxygen, not on vents or CPAP, who are 36 weeks of age. Please note that all such infants have ALREADY BEEN DIAGNOSED as BPD on NG07.

It is only these infants who now require further explanation. They can be challenged or not. Those challenged pass or fail and have the diagnosis of BPD assigned as per the challenge.

I would thus suggest that we may not need such a flow diagram.

Let me know your thoughts.

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, September 14, 2006 12:02 PM
To: Neil Finer
Cc: Das, Abhik; Poole, W. Kenneth
Subject: BPD definition for SUPPORT

Hi Neil,

Attached is a flow chart describing a scheme for determining BPD for SUPPORT infants. The definition described is based primarily on the physiologic definition, with data from the NG07 and NG03 used to fill in the gaps. This definition was modified from the one used for the Benchmarking study (which had slightly different data available). Please look this over and let me know what you think, and if you think we should get additional input (such as from Michele Walsh). In addition, please review the assumptions made in the flowchart, listed on the second page of the document.

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

From: Nancy Peters
To: Higgins, Rosemary (NIH/NICHD) [E]; Michael O`Shea
Cc: Das, Abhik; Gantz, Marie
Subject: RE: SUPPORT ROP DATA
Date: Wednesday, September 20, 2006 10:35:44 AM

It is on my "to do" list. I will need to retreive this information from the opth office charts....what I need was not in the medical record, only a visit summary.

Nancy

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 10:17 AM
To: Michael O`Shea; Nancy Peters
Cc: Das, Abhik; Gantz, Marie
Subject: SUPPORT ROP DATA

20	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

The above table shows missing ROP information needed for outcome for SUPPORT. Can you check to see if you have this information?

Thanks for all the hard work!!
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: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Michael Cotten; goldb008@mc.duke.edu; Gantz, Marie
Subject: Re: SUPPORT ROP DATA
Date: Wednesday, September 20, 2006 10:25:40 AM

Thanks, Rose. We're on it!
Kathy

Kathy J. Auten, MSHS
NICHD Neonatal Research Network Coordinator
Duke University Medical Center
Box 3179
Bell Building, Room 141
Durham, NC 27710 USA
919-681-5859 tel
919-681-4868 fax
kathy.auten@duke.edu

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> wrote on 09/20/2006 10:15:31 AM:

> 19
>
> [redacted]
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
> [redacted]
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
> [redacted]
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
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> [redacted]
>
> 50 weeks PMA has been reached and final ROP exam status has not been
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> 19
>
> [redacted]
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> [redacted]
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>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
>
> 19
>
> (b) (6)
>
> No SUPP10 records have been entered even though SUPP09 Question C1
> indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
>
> 19
>
> (b) (6)
>
> 50 weeks PMA has been reached and final ROP exam status has not been
> reported on the SUPP10 for either eye.
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> The above table shows missing ROP information needed for outcome for
> SUPPORT. Can you check to see if you have this information?
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> Thanks for all the hard work!!
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>
> 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
> (For overnight delivery, use Rockville, MD 20852)
> 301-435-7909
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov
>

From: Walsh, Michele
To: Wade Rich; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Wednesday, September 20, 2006 10:23:38 AM

Wade: I entirely agree: the dreaded RA nc has crept in to our unit. I think these kids are contaminating the data.
From the initial physiologic definition data, 99% of the kids still on oxygen later in their course were on nc. Of these, fully 76% were receiving an effective FiO2 <= 23%. Those with sats >96% in these cannulas were successful
in weaning to RA- at least for the short duration of the nc.
Alternatively, as you suggest: in our unit we are very comfortable with hyperoxia, and exquisitely attuned to avoiding
hypoxia!!
Michele

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, September 20, 2006 10:05 AM
To: Walsh, Michele; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: Neil Finer; higginsr@mail.nih.gov
Subject: RE: Oximeter data for the SUPPORT Trial

Michele,

It occurs to me that if many others are using a strategy which precludes weaning in infants who are in "effective" FiO2 of .21 we are including that entire group in our data, even though
unit practice does not allow for weaning them.

1) Would you wean an infant in 30% on 25cc/min if his sat was >95, or defeat his alarm?
2) Do you have a feel from your data how many infants that represents in this population?

I believe the other issue that needs to be tightly defined in each center is how saturation is maintained in the nasal cannula infant. This may sound obvious, but it is not. If a NICU does not
use blenders, than all weaning must be by flow, which is crude, and makes it difficult to maintain a tight sat range. If the NICU uses blenders, than the question of when to use flow and when to use
FiO2 must be clearly addressed, as well as when to stop weaning and attempt R/A. I believe than most centers do not look as critically at saturation later in the course of these infants, and as such
have not made these criteria strict. Certainly any nurse or therapist who floats into the NICU or comes from a labor pool will not instinctively feel guilty about defeating high alarms in this population.

Food for thought.

wade

From: Walsh, Michele [mailto:Michele.Walsh@uhhs.com]
Sent: Wednesday, September 20, 2006 4:10 AM
To: Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Neil: Format looks great. Look forward to receiving it!
I'm interested in any thoughts about reducing hyperoxia beyond 14 days.

Michele

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tue 9/19/2006 8:29 PM
To: Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
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Subject: RE: Oximeter data for the SUPPORT Trial

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1. Recruitments
2. The format of Oximeter data to send to the sites (See attachment as an Example)
3. Other issues
Please let me know if you want to add items to this agenda.
Thanks
Neil

CELEBRATING 140 YEARS of Caring for Cleveland.

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR 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: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook
Cc: Das, Abhik; Gantz, Marie
Subject: RE:
Date: Wednesday, September 20, 2006 10:20:01 AM

We are following both these patients.

(b) (6) - was a " no show" for an appointment on 7/26/06 and has not rescheduled yet.

(b) (6) - Zone II, Stage O on 08/10/07. Next appointment on 02/15/07.

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 20, 2006 10:12 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook; Angelita Hensman
Cc: Das, Abhik; Gantz, Marie
Subject: RE:

One more also

14	(b) (6)	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, September 20, 2006 10:12 AM
To: alaptook@WIHRI.org; 'Angelita Hensman'
Cc: 'Das, Abhik'; Gantz, Marie
Subject:

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From:	Abbot Laptook
To:	Wally Carlo, M.D.; Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; poo@rti.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Wednesday, September 20, 2006 9:39:21 AM

Neil
I agree that this looks good. I would be in favor of separating days 1-14 from day 15 thru 36 weeks. AL

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 20, 2006 8:04 AM
To: Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; adas@rti.org; mgantz@rti.org; poo@rti.org; Abbot Laptook
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Neil:

Looks great! Does the "through 36 weeks" exclude 1-14 days?

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wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Email: wcarlo@peds.uab.edu

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From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, September 19, 2006 7:30 PM
To: Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
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1. Recruitments
2. The format of Oximeter data to send to the sites (See attachment as

an Example) 3. Other issues Please let me know if you want to add items to this agenda.
Thanks
Neil

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Gantz, Marie
Subject: RE: NICHD NRN Support Study Masimo oximeters
Date: Tuesday, September 19, 2006 2:04:07 PM

I don't think the data tells us anything about the histograms that are displayed. Wade's email seemed to indicate that the ones he looked at had the right skew but were outputting wrong histograms. It is probably safe to assume that the Miami batch has the same problem and send them on to Irvine for them to rectify as necessary, unless that presents a big disruption. Marie has looked at the data from these oximeters and though it is difficult to be definitive, it does appear that they are correctly skewed.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 19, 2006 1:59 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: Fw: NICHD NRN Support Study Masimo oximeters

It is not clear to me whether or not they have the altered histograms??
Can massimo tell or can Marie tell from the data?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Maribeth Sayre <MSayre@masimo.com>
To: Zaterka-Baxter, Kristin <kzaterka@rti.org>; Chris Novak <CNovak@masimo.com>; Vicki Bishop <VBishop@masimo.com>; George Yaghnam <GYaghnam@masimo.com>
Cc: Das, Abhik <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Sep 19 13:40:48 2006
Subject: RE: NICHD NRN Support Study Masimo oximeters

<<RMA Form.doc>>
Hi Kristin,

The easiest way to test the oximeters is to set the simulator at 90%.
The oximeter should read either 93 or 87.
I don't know why these oximeters have the standard histogram instead of the SUPPORT histogram.
The good news is that our process has changed, so this should not be a problem in the future.
To change the histograms, please send the oximeters back to Irvine. You will need to call for a RMA#, fill out the attached form noting that these are masked oximeters that need to have the histogram changed to the SUPPORT histogram, and send to the attention of Chris Novak.

Masimo will pay the shipping charges.

Thanks,
Maribeth

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, September 18, 2006 10:37 AM
To: Maribeth Sayre; Chris Novak; Vicki Bishop
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: NICHD NRN Support Study Masimo oximeters

Hi Marybeth,

Please find below masimo oximeter serial numbers of instruments found recently to have seemingly normal histogram ranges instead of the skewed ranges required for the masked NRN Support study. These are not new oximeters but instead have been recently moved from our Miami site to the University of Alabama site where the histogram ranges were notice to be different than what was viewed on their current oximeters of the same color code. We're not sure if this has affected the data in any way or if it's something that's possibly just incorrect on the visual screen. We are in the process of trying to test one of these oximeters with an oximeter simulator but this will not take place until tomorrow at the earliest.

These are the oximeters that were originally sent to the University of Miami on April 7, 2005.

317219

317312

317363

317393

317408

317420

317431

317443

These are the histogram ranges on the Miami Masimo's and our UCSD study coordinator has told me these are also the standard for Masimo's off the shelf.

96-100%

91-95%

86-90%

81-85%

<85%

Please let me know if you need further information to look into this matter; I'd be happy to send you whatever is needed.

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Gantz, Marie
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT primary outcomes update
Date: Tuesday, September 19, 2006 1:01:06 PM
Attachments: Infants with missing ROP 9-19-06.xls

Hi Rose,

Attached is an Excel spreadsheet with the center and network numbers for 74 patients missing the ROP diagnosis. Each center was sent a missing ROP report on these infants earlier this month. If you would prefer the list in another format (like in a Word document), please let me know and I will send it to you.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 15, 2006 2:08 PM
To: Gantz, Marie; nfiner@ucsd.edu
Cc: das@rti.org
Subject: RE: SUPPORT primary outcomes update

If it is ok with Ahbik, I would like a list of patient numbers and center number with the missing ROP outcome. I can gently remind the PI's that we need to have this info for the first DSMC look at the data. WE really should have the data.

Thanks
ROSE

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 15, 2006 1:18 PM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: das@rti.org
Subject: SUPPORT primary outcomes update

Neil and Rose,

I received Neil's comments on the BPD definition, and will look at them more closely on Monday when I am back in the office (I am off-site

attending a class today). However, I wanted to give you some idea of how close we are to the first interim analysis for SUPPORT. Using the attached definitions of BPD and ROP, we currently have final outcomes (survival without BPD/ROP) for 211 SUPPORT infants. We have about 75 additional infants who have known BPD but unknown ROP. The centers have been receiving monthly missing forms reports listing infants who have reached 50 weeks PMA but are missing ROP final status (last month there were 79 missing and this month there were 74). Almost all of these infants (67) have had at least one ROP exam, but final status has not been reached as defined in the SUPPORT MOP. It is possible that for some of these infants we will receive additional exam data, but only three have had exam data entered since April.

Obviously, if we had ROP outcomes on these infants we would be much closer to being able to do the first interim analysis of the data (which requires outcomes on 328 infants). So, I am wondering if you have any ideas regarding how to treat these missing ROP outcomes. We have NG03 ROP data on most of the infants, but for all but a couple, it is data from the 2002 version of the form. We might be able to make some ROP determinations using this data if the ROP criteria from the new NG03 are applied, but they are slightly different from those listed in the SUPPORT MOP. Even if we do use the NG03 data, it looks like 50-60 infants will fall into the undetermined category.

Please let me know if you have any thoughts on this issue.

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

Center	Network	Missing ROP error message
03	(b) (6) [redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
03	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
03	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
03	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for the right eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
08	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
09	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
11	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
11	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
13	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
14	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	No SUPP10 forms have been entered though 50 weeks PMA has been reached and the infant did not die early.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
16	[redacted]	SUPP10 records have been entered for prior to study status, but SUPP09 Question C1 indicates that no exam for ROP was performed.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

18	(b) (6) [redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
18	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
19	[redacted]	No SUPP10 records have been entered even though SUPP09 Question C1 indicates that an exam for ROP was performed. 50 weeks PMA has been reached.
19	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
20	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
21	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.
22	[redacted]	50 weeks PMA has been reached and final ROP exam status has not been reported on the SUPP10 for either eye.

From: Zaterka-Baxter, Kristin
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Masimo to you
Date: Tuesday, September 19, 2006 10:45:57 AM

I think we're ok with keeping them quaranteened for now until we here from Masimo. I believe there are only 8 oximetes in question.
Thanks,
Kris

-----Original Message-----
From: Das, Abhik
Sent: Tuesday, September 19, 2006 10:12 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin
Subject: RE: Masimo to you

Sounds like it. Would Masimo be able to confirm this and correct the histogram business? Till then, unless we have a shortage, maybe we should still keep them quaranteened?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 19, 2006 9:44 AM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: Fw: Masimo to you

Looks like we are ok. Sounds like we can "un-quaranteen" them, right?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wade Rich <wrich@ucsd.edu>
To: Monica Collins <MCollins@peds.uab.edu>; Maribeth Sayre <MSayre@masimo.com>; Neil Finer <nfiner@ucsd.edu>
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>; Das, Abhik <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Sep 19 09:45:00 2006
Subject: RE: Masimo to you

Monica, et al.

I did a simulation this AM and the SUPPORT oximeters with the "off-the-shelf" histogram instead of the SUPPORT histogram are still skewed oximeters. This means, in a pinch, you could use them. I will pursue getting the histograms changed.

Wade

Maribeth,
These are the 10 late ones you sent to UAB. Maybe when they swapped the boards they forgot to change the histogram to ours.
w

From: Monica Collins [mailto:MCollins@peds.uab.edu]
Sent: Friday, September 15, 2006 11:51 AM
To: Wade Rich
Subject: Masimo to you

Dude,
One masimo coming your way--let me know what you think.
Monica

UPS Tracking # 46848741128

From: Michael Cotten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Sandra G. West
Subject: Re: Genomics
Date: Tuesday, September 19, 2006 10:16:01 AM
Attachments: Sample labeling by RTI for transfer.doc

---

thanks Rose....I"m cc'ing the bank manager at CHG on this email to let them know what's happening. ....I need to wait on sending the revised protocol to all sites until I get the okay from rti and chg that the plan i've proposed is feasible....I think rti is okay w/ it....i need to get chg's okay too....

here's the proposed plan:

(See attached file: Sample labeling by RTI for transfer.doc)

thanks

mc

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

To: <cotte010@mc.duke.edu>
cc:
Subject: Re: Genomics

09/19/2006 09:50 AM

Do you have a revised protocol for irb approval at the sites to include all of the remaining blood? Some of them need to go back to the irbs (which can take 1-2 months under ideal circumstances)?
I will send this is the am to the subcommittee.
shall I get a call set up for the labeling procedure?
Thanks for all the effort.
Rose

Sent from my BlackBerry Wireless Handheld

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

From: Michael Cotten <cotte010@mc.duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg <goldb008@mc.duke.edu>
Sent: Tue Sep 19 09:47:06 2006
Subject: Re: Genomics

Hi Rose,

here's the latest MOP

(See attached file: mop 9-19-06.doc)

I have talked w/ the RTI data people and CHG data people about the labeling strategy for samples that will be described in the revised protocol. They are both taking a look at a proposal to have RTI place CHG derived stickers on the filter cards, and the rest of the card removed....so chg gets the blood spot cards, each with and individual sticker/bar code, that will be linked to a new study number generated by RTI. RTI will keep a log linking the new study number and the chg # at RTI....the log linking the new study number w/ the original will be deleted once the new labels are affixed to the cards and double checked.

I have told Abhik and CHG bank manager Sandra West that we must go through you to discuss any plans for handling/mailing of samples before contact is made with the storage site.....

thanks

cm

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

09/19/2006 08:11 AM

To: <cotte010@mc.duke.edu>
cc: <goldb008@mc.duke.edu>
Subject: Genomics

Mike
Can you distribute the MOP to the genomics subcommittee? (Or send it and I can do it tomorrow). Also, did you finalize the protocol to get all of the leftover blood so we can send it to the sites? Some need to go back to the IRB.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

Sample labeling by RTI for transfer from Storage Site to CHG
9-19-06

Summary of sample ascertainment. RTI will use a pre-printed Sample Acquisition form (SAF) that is assigned to the individual sample card. These SAF's are pre-printed with currently 20 short and 4 long bar code labels. In many of the studies Duke CHG supports, if blood tubes are to be frozen before shipping to the DNA bank, the long strips are used to create a "flag". That way, when samples are checked in to the DNA bank, the new sequential sample number label can be attached to the '"flag" without thawing the tube. The label media is tear-resistant, the ink is waterproof and smear-proof, and the glue is rated to -80° C. The pre-printed numbers are sequential, and therefore every sample has a unique identifier. These can be tailored to this NICHD study, utilizing only short labels affixed to the filter paper spots. We will use a separate SAF for each filter card, so any one child may have 4 SAF's, one for each filter paper card.

RTI will fill in the handwritten SAF form that will link the newly assigned study number with the CHG SAF number. These handwritten forms, one for each filter paper sample, will remain at RTI.

In addition to the handwritten SAF form which is maintained at RTI, RTI will enter information about the sample into the CHG Clinical Applications (CLINAPPS) Sample Acquisition Form Entry program (see example, figure 1 below). This form allows RTI to be linked to information about the status of sample from the card within the CHG, and allows CHG to be able to match expected samples with received samples with the correct SAF number on arrival.

To complete the ascertainment of a sample on written and electronic SAF's:

- The new study number (N2) is handwritten on the RTI SAF form to assure the identity of the sample to the RTI. (The N2 is NOT transferred on the electronic SAF to the CHG.) The handwritten SAF form stays at RTI.
- The study identifier, the patient identifier (consisting of a center code (RTI would be center of origin for all samples), family number (unique number assigned to each filter paper card), and gender are entered in the appropriate boxes on the electronic form.
- A numbered label from the SAF is affixed to the appropriate filter paper card (the SAF#)
- A notation is made on the form as to how many spots are on the card.

For this study, the DOB is not entered. The information entered from the SAF is transferred to the database, **but WITHOUT any NAME or Personal identifier INFORMATION or dates.** This information, tailored to this study, is secured by several levels of password and network security within CHG. After entry, a status report of the site's entire SAF entry is given in a summary table available to RTI and the CHG Database administrator.

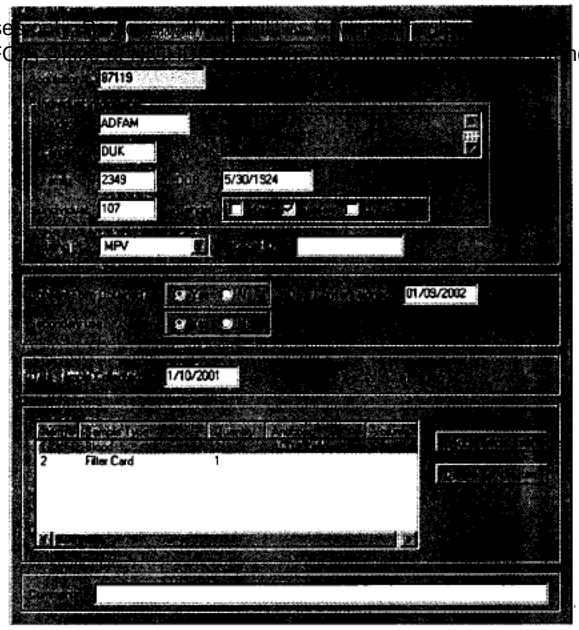

Figure 1. Example of sample acquisition form (SAF) electronic entry version. These forms can be tailored for specific studies, with more or less information as needed.

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Infant Demise
Date: Monday, September 18, 2006 4:20:51 PM

Sorry; looked at the UTH in the email address and thought it was Utah, just got off the phone with them about reporting a medwatch.
Thanks,

Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 18, 2006 4:18 PM
To: Zaterka-Baxter, Kristin
Subject: Re: Infant Demise

Kris
This is Houston, not Utah

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Lis, Anna E <Anna.E.Lis@uth.tmc.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn <petrie@rti.org>
Sent: Mon Sep 18 16:12:16 2006
Subject: RE: Infant Demise

Hi Anna,

Thank you for the notification. Just wanted to clarify; is this for the Support study infant Susan Tepper reported over the phone? We discussed completing the Medwatch form for this infant as well.

Thanks again,

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Lis, Anna E [mailto:Anna.E.Lis@uth.tmc.edu]
Sent: Monday, September 18, 2006 3:45 PM
To: higginsr@mail.nih.gov; Petrie, Carolyn
Cc: Zaterka-Baxter, Kristin
Subject: FW: Infant Demise

From: Lis, Anna E
Sent: Monday, September 18, 2006 12:38 PM
To: Kwape, Bonang
Cc: Riggs, Marianna
Subject: Infant Demise

This is notification that Pt (b) (6) -1 expired on (b) (6)

The Pt. was enrolled in : HSC-MS-04-415 & HSC-MS-05-0218.

The death was unexpected & we do not believe the death was study related.

Thank you,

Anna Lis, RN

Senior Research Nurse

713-500-5729

From: Webb, Robin E.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Call for Oximeter data for the SUPPORT Trial
Date: Monday, September 18, 2006 4:15:54 PM

After some adjusting of schedules, the call to discuss the Oximeter data for the SUPPORT Trial WILL be held on Thursday, 9/21 please note the new time:

Thursday, September 21
1:00pm ET

Dial:
Outside the USA
1-203-310(b) (6)
or
Within the USA
866-675(b) (6)

Then, enter Participant Passcode:
(b) (6)

Please let me know if you have any questions.

Thanks,
Robin

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT approved
Date: Monday, September 18, 2006 2:57:33 PM

Not yet; Wade is out of the office until tomorrow so he can't check the masimo with his oximeter simulator UAB sent to him on Friday. I've not received a reply from any of the 3 people I emailed this afternoon at masimo nor have I gotten a call back from Maribeth Sayre, Masimo liaison for the Support trial.....I'll keep trying.
Thanks,
Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 18, 2006 2:48 PM
To: Zaterka-Baxter, Kristin
Subject: Re: SUPPORT approved

Do we know yet if the Miami ones were "rigged" correctly?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 18 14:46:23 2006
Subject: RE: SUPPORT approved

No, the ones from Miami are not being uses and have been put aside for the time being. The 10 being sent to NM from UAB are the 10 newer ones that came directly from Masimo - sorry for the confusing email below.
Thanks

Kris

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 18, 2006 2:43 PM
To: Zaterka-Baxter, Kristin
Subject: Re: SUPPORT approved

So am I to understand that the blue Miami oximeters are ok?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 18 14:40:51 2006
Subject: FW: SUPPORT approved

Hi,

FYI below. I'm planning on sending 10 (5 blues and 5 oranges) from UAB to NM. These are the newer ones where we had to check the versions per Wade (version 4) and are apparently programmed properly. We've essentially quarantined the blue masimos from Miami for the time being which are the ones NM was supposed to get.

Also, Houston is sending Tufts 4 blues and Utah has sent Stanford 3 blues and 3 oranges.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
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Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]
Sent: Monday, September 18, 2006 2:31 PM
To: Zaterka-Baxter, Kristin
Cc: Kristi Watterberg
Subject: RE: SUPPORT approved

Kris,
Here is the approval letter and approved consent. We included breathing outcomes and growth protocols. We started to include antenatal consenting but it was decided that it was actually just internal record keeping to document time and effort and did not represent research. We will, therefore, complete the antenatal consenting paperwork without consent. We will present the MRI protocol separately.

Assuming that it takes one week to get monitors, and hoping for 2 - 3 <28 week deliveries/week, I think 2 monitors of each color (4 total) should be adequate. If we get triplets, I will panic! I can't remember the last time we had <28 week triplets.
Thanks,
Connie

Conra (Connie) Backstrom Lacy
Research Nurse Manager
(505) 272-0367
pager (505) 951(b) (6)
fax (505) 272-6845
cbackstrom@salud.unm.edu

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 9/18/2006 12:03 pm
>>>
Not clueless at all....! I will be asking one of our sites to send
you
masimo study oximeters. We're planning on using the one's the Network sites have already purchased. Maribeth Sayer is the Masimo Director of Medical Affairs and the Masimo liaison for the Support study. I'm

going
to forward you a contact email for her. I believe it's up to your site whether or not to wait until after her visit to begin accrual but to my
knowledge, none of the other 3 newer sites have requested a visit from Masimo, rather one of our PIs from an enrolling center has come for a site visit and to help with study start up and things needing attention.
I would refer you to Rose who is better suited to answer that question.

How many oximeters do you anticipate needing? Their treatment assignments will be coded as blue or orange to correspond with the randomization cards. For each potential subject you will need one of each on hand.

Please fax/email a copy of your approval and consent (Congrats!!!!) and
let me know of you have rolled in the secondary studies into the main trial consent or if you will have stand alone consents for these studies.

I will send you the randomization box tomorrow; I need to line up the oximeter transfer first.

Thanks, and please let me know if you have any other questions.

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]

Sent: Monday, September 18, 2006 1:15 PM
To: Zaterka-Baxter, Kristin
Cc: Kristi Watterberg
Subject: SUPPORT approved

Kris,

We have been approved by the IRB and the GCRC to conduct the SUPPORT

study. We are ready for randomization envelopes and monitors. I got
a

call on September 3rd from Julie Bradley in Phoenix wanting to
schedule

Dr. Mary Beth Sayer (of Masimo) to come for a site visit. I returned

her call and gave her my pager number. I have not heard from her
again

and have only reached her voice mail. Do they bring, or send, the

monitors or do we get them from Rose? Who is Dr. Sayer? Do we need
to

wait for her visit?

Sorry to be so clueless!

Thanks,

Connie

Conra (Connie) Backstrom Lacy

Research Nurse Manager

(505) 272-0367

pager (505) 951-(b) (6)

fax (505) 272-6845

cbackstrom@salud.unm.edu

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT approved
Date: Monday, September 18, 2006 2:40:53 PM
Attachments: 06-283 Watterberg approval ltr.pdf
Approved06-283 Watterberg UNMHSC CF v8-30-06.doc

Hi,
FYI below. I'm planning on sending 10 (5 blues and 5 oranges) from UAB to NM. These are the newer ones where we had to check the versions per Wade (version 4) and are apparently programmed properly. We've essentially quarantined the blue masimos from Miami for the time being which are the ones NM was supposed to get.

Also, Houston is sending Tufts 4 blues and Utah has sent Stanford 3 blues and 3 oranges.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]
Sent: Monday, September 18, 2006 2:31 PM
To: Zaterka-Baxter, Kristin
Cc: Kristi Watterberg
Subject: RE: SUPPORT approved

Kris,
Here is the approval letter and approved consent. We included breathing outcomes and growth protocols. We started to include antenatal consenting but it was decided that it was actually just internal record keeping to document time and effort and did not represent research. We will, therefore, complete the antenatal consenting paperwork without consent. We will present the MRI protocol separately.

Assuming that it takes one week to get monitors, and hoping for 2 - 3 <28 week deliveries/week, I think 2 monitors of each color (4 total) should be adequate. If we get triplets, I will panic! I can't remember the last time we had <28 week triplets.
Thanks,
Connie

Conra (Connie) Backstrom Lacy
Research Nurse Manager
(505) 272-0367
pager (505) 951(b) (6)
fax (505) 272-6845

cbackstrom@salud.unm.edu

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 9/18/2006 12:03 pm
>>>
Not clueless at all....! I will be asking one of our sites to send you masimo study oximeters. We're planning on using the one's the Network sites have already purchased. Maribeth Sayer is the Masimo Director of Medical Affairs and the Masimo liaison for the Support study. I'm going to forward you a contact email for her. I believe it's up to your site whether or not to wait until after her visit to begin accrual but to my knowledge, none of the other 3 newer sites have requested a visit from Masimo, rather one of our PIs from an enrolling center has come for a site visit and to help with study start up and things needing attention.
I would refer you to Rose who is better suited to answer that question.

How many oximeters do you anticipate needing? Their treatment assignments will be coded as blue or orange to correspond with the randomization cards. For each potential subject you will need one of each on hand.

Please fax/email a copy of your approval and consent (Congrats!!!!) and let me know of you have rolled in the secondary studies into the main trial consent or if you will have stand alone consents for these studies.

I will send you the randomization box tomorrow; I need to line up the oximeter transfer first.

Thanks, and please let me know if you have any other questions.

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

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kzaterka@rti.org

-----Original Message-----
From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]
Sent: Monday, September 18, 2006 1:15 PM
To: Zaterka-Baxter, Kristin
Cc: Kristi Watterberg
Subject: SUPPORT approved

Kris,

We have been approved by the IRB and the GCRC to conduct the SUPPORT

study. We are ready for randomization envelopes and monitors. I got
a

call on September 3rd from Julie Bradley in Phoenix wanting to
schedule

Dr. Mary Beth Sayer (of Masimo) to come for a site visit. I returned

her call and gave her my pager number. I have not heard from her
again

and have only reached her voice mail. Do they bring, or send, the

monitors or do we get them from Rose? Who is Dr. Sayer? Do we need
to

wait for her visit?

Sorry to be so clueless!

Thanks,

Connie

Conra (Connie) Backstrom Lacy

Research Nurse Manager

(505) 272-0367

pager (505) 951(b) (6)

fax (505) 272-6845

cbackstrom@salud.unm.edu

THE UNIVERSITY OF NEW MEXICO ♦ HEALTH SCIENCES CENTER
SCHOOL OF MEDICINE

Human Research Review Committee
MSC 08 4560 BMSB Room B71
1 University of New Mexico~Albuquerque, NM 87131-0001
(505) 272-1129 Facsimile (505) 272-0803
http://hsc.unm.edu/som/research/hrrc/

9/5/2006
Kristi Watterberg, MD
Pediatrics Neonatology Division
MSC: 10 5590
Albuquerque, New Mexico 87131

SUBJECT: HRRC Approval of New Research Protocol
HRRC#: 06-283
Study Title: The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) NICHD Neonatal Research Network
Type of Review: Full Committee Review
Approval Date: 01-Sep-2006
Expiration Date: 14-Aug-2007

Dear Dr. Watterberg:

The Human Research Review Committee (HRRC) has reviewed and approved* the above-mentioned research protocol including the following:

HRRC Application received 8/21/2006
UNMHSC Consent Form v8/30/2006
Grant Application received 8/7/2006
Surfactant NICHD Protocol 3/28/2005
Breathing Outcomes NICHD Protocol 12/6/2005
Oxygen Saturation NICHD Protocol 1/26/2006
UNMHSC HIPAA Form v8/7/2006

Consent decision:
Requires a signed consent form
HIPAA Authorization on record; signed HIPAA required

Sincerely,

William P. Reed

William Reed, M.D.
Executive Chairman
Human Research Review Committee

* Under the provisions of this institution's Federal Wide Assurance (FWA00003255), the HRRC has determined that this proposal provides adequate safeguards for protecting the rights and welfare of the subjects involved in the study and is in compliance with HHS Regulations (45 CFR 46), FDA Regulations (21 CFR 50, 56).

HRRC FACT SHEET

Accessing Forms: **All forms may be accessed on the HRRC website at http://hsc.unm.edu/som/research/hrrc/. Frequent changes are made to HRRC forms; therefore it is recommended that you do not save forms on your personal computer for future use.**

Consent/Assent Form(s): **When consent is required, it is the responsibility of the principal investigator (PI) to ensure that ethical and legal informed consent has been obtained from all research participants. A date stamped original of the HRRC approved consent form (s) is attached, and copies should be used for enrolling participants during the above approval period.**

Continuing Review: **To comply with federal law, the HRRC must conduct continuing review of this research before the expiration date noted above. It is the responsibility of the PI to submit a progress report to the HRRC at least 30 days prior to the end of the approval period in order for this study to be considered for continuation. An electronic copy of the current protocol, which has been updated to reflect all amendments and changes made to the research, must be submitted with the Progress Report and should be sent electronically to HRRC@salud.unm.edu.**

Amendments and Changes: **Investigators are not permitted to implement any amendments to this protocol or changes to the consent form(s) without prior approval of the HRRC. In situations where changes are made to eliminate apparent immediate hazard to the subjects, the HRRC should be notified of the change immediately.**

Adverse Events: **Adverse events or unexpected problems must be reported to the HRRC in accordance with the HRRC adverse event policy at http://hsc.unm.edu/som/research/hrrc/MANUAL.html#eighttwo.**

Correspondence: **Please reference the HRRC # and study title in all documents and correspondence related to this protocol. All HRRC correspondence is considered source documents and must be maintained with the research records.**

Study Closures: **To close a study, a Closure Report must be submitted to the HRRC. In the event the PI has received a request for Progress Report and local research activities are complete, the Progress Report, indicating the PI's request to close the study, should be submitted in lieu of the Closure Report.**

HIPAA Authorization Addendum: **Although federal regulations do not require HRRC approval of HIPAA research authorization forms, the HRRC requires the HIPAA authorization addendum as supporting documentation with new studies and continuing review submissions. HIPAA Authorization addenda undergo an "administrative" review, but are not subject to HRRC approval. Therefore, HIPAA authorization addenda are not stamped with approval/expiration dates, nor are they returned to the principal investigator. If HIPAA Authorization is required, the HIPAA Authorization version noted in the approval letter must be signed in conjunction with the consent form.**

The University of New Mexico Health Sciences Center
Consent to Participate in Research

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

Your child is invited to participate in a research study being done by Kristi Watterberg. M.D., who is the Principal Investigator, and her associates, from the Department of Pediatrics. This research is 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.

Since 1970 two basic ways to help premature babies breathe have been used in Newborn Intensive Care Units. One method, called "intubation," involves placement of a breathing tube in the infant's airway and attaching it to a machine called a "ventilator" which breathes for the infant. The other method, called "CPAP" or "Continuous Positive Airway Pressure," involves placement of short tubes in the infant's nose and providing air pressure which helps the infant breathe on his/her own. Many studies have been done to see how to make these two methods work as well as possible. Research has shown, however, that all babies who need help with breathing are at risk of developing a type of chronic, or long lasting, lung disease called "Bronchopulmonary dysplasia," or "BPD" for short. Oxygen is also used whenever a baby is not able to get enough oxygen into his/her blood by breathing room air. Doctors know that it is important to be sure a baby is getting enough, but not too much oxygen. One possible complication of too much oxygen is an eye disease called "Retinopathy of Prematurity," or "ROP," that may result in poor vision or even blindness. Since 1990 a medication, called "surfactant" has been available to help premature babies breathe easier, but a tube must be placed in the airway to give this medicine. All of these treatments have been carefully studied and all are used in Newborn ICUs. This is the first study to carefully compare the use of all of these methods starting from the first moments after birth and following the babies until at least 18 months after they would have been born, if they had not been premature.

In this study, infants who receive delivery room CPAP and who have specific guidelines for having a breathing tube placed will be compared to infants who have a breathing tube placed and surfactant given in the delivery room or very soon after birth. The study will also compare keeping a lower range (85-89%) or a higher range (91-95%) of oxygen levels in the blood (saturation). Both of these ranges are within the oxygen saturation range that is currently used for premature infants in the NICU at UNM Hospital (85 – 95%). An alarm will sound if the oxygen saturation goes above or below that range, the same as for other premature infants in our NICU. While it is known that higher oxygen ranges are associated with more eye disease, the safest oxygen range is still unknown. We hope to find out if a lower range results in less ROP (Retinopathy of Prematurity).

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). About 30 babies will take part in this study at the University of New Mexico. 1300 babies will participate in this study across the United States. The National Institutes of Health is funding this study.

This form will explain the research study, and will also explain the possible risks as well as the possible benefits to you. We encourage you to talk with your family and friends before you decide to take part in this research study. If you have any questions right now, please ask one of the study investigators.

What will happen if I decide to participate?

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 treatments. 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 or right after arrival in the NICU, 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. Your baby's doctors will make that decision if they think it is necessary for your baby. Studies have suggested that babies who have a breathing tube placed and surfactant given very early may benefit from the surfactant (some studies have shown that very early surfactant results in less "air leak", where air escapes from the air spaces of the lungs into the area around the lungs and less death, but other studies have not found this difference), but they may have a higher risk for developing BPD because of the breathing tube. On the other hand, infants treated with early CPAP may not receive the early benefit of surfactant, but may have a lower risk for developing BPD because no breathing tube is inserted. It is not known which of these breathing treatments is better.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomly assigned to having an oximeter (a machine that monitors oxygen in the blood) which reads slightly high or one that reads slightly low. The oximeters used in this study are FDA approved devices which have been adjusted for research purposes to show an oxygen saturation value which is either a little higher or a little lower than the true oxygen reading when the oxygen is in the normal range (between 85 and 95%). Outside the normal range, the oximeter shows the true oxygen level. This will help to protect your baby from oxygen levels that are too high or too low

Your infant will be assigned to one of the four groups shown below. Neither you nor your baby's doctors will know which oxygen saturation range is being targeted; however, the alarm limits will remain the same as for all premature infants in our NICU. Your baby will not be exposed to lower or higher oxygen saturations than are currently accepted for all premature infants in our NICU. The assignments will be made randomly, like the flip of a coin.

CPAP Higher oxygen level in the blood	CPAP Lower oxygen level in the blood

Breathing tube + breathing machine + surfactant Higher oxygen level in the blood	Breathing tube + breathing machine + surfactant Lower oxygen level in the blood

All the rest of your infant's care will be the standard treatments for premature babies in the UNM Children's Hospital NICU. Information about that care and certain results, such as head ultrasounds and growth measurements, will be collected from your child's medical record. All children who participate in the project will be invited to return to Special Baby Clinic at 6 month intervals during the first two years as part of their routine care. At those visits, or by telephone if you are not able to come to clinic, we will ask you 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 questions about family history of breathing problems, and questions about your home, including things that may increase your child's risk of breathing problems. It will take about 15 minutes to answer these questions. 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.

How long will my child be in this study?

Study guidelines for lung treatments of infants in both groups will be followed for two weeks. 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. The early part of the project will last until the end of your child's hospital stay. In order to evaluate the long term effects of the treatments in this study, information will be collected 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. Kristi Watterberg and her 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 UNM Children's Hospital's Special Baby Clinic with their child when (s)he is 18 months of age.

What are the risks or side effects of being in this study?

Participation in this study may involve some added risks or discomforts. Each of these treatments has some risk. Some unknown risks may be learned during this study. All of these treatments are currently clinically accepted, but haven't been compared with each other in this manner, so it is hard to predict which group may do better. If your baby is assigned to the group of babies who have a breathing tube placed and surfactant given very early, he/she may benefit from the surfactant, but may have a higher risk for developing BPD because of the breathing tube. If your baby is assigned to the CPAP group, he/she may not receive the early benefit of surfactant, but may have a lower risk for

developing BPD because no breathing tube is inserted. Both groups of babies will receive positive pressure to their airways. This is the usual clinical practice for almost all babies who are this premature (about 90% at UNMH). The CPAP mask can cause a low heart rate. If this happens, the mask is removed and repositioned. CPAP can cause air to collect in the stomach, so a small tube is placed from the mouth into the stomach. All babies are monitored for these problems. Positive pressure may increase the risk for air to escape from the lungs into the area around the lungs (air leak). This could require draining the air with a tube inserted into the chest. "Air leak" happens commonly in very premature infants, usually because of their underdeveloped lungs. It can happen with CPAP or a breathing tube. It can even happen when a baby does not have any extra pressure to help their breathing.

For this study, there will be no change in the oxygen saturation range from the one that is currently used in the NICU at UNMH. The specific and ideal oxygen range to reduce eye disease is unknown. We hope that this study will help to determine if a lower or higher oxygen range may be better. The higher and lower ranges that are used in this study are both in the oxygen range that is currently used for all babies admitted to the UNM NICU. 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.

What are the benefits to being in this study?

Your child may or may not be benefit from participating in this study. The knowledge learned from this study may help us treat babies in the future.

What other choices do I have if I do not want to be in 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 as needed. This may include oxygen and help to breathe that is similar to the treatments in this study.

How will my information be kept confidential?

We will take measures to protect your privacy and the security of all your personal information, but we cannot guarantee confidentiality of all study data.

Information contained in your study records is used by study staff and, in some cases it will be shared with the sponsor of the study. The University of New Mexico Health Sciences Center Human Research Review Committee (HRRC) that oversees human subject research, the National Institutes of Health which sponsors this study, and the Food and Drug Administration and/or other regulatory entities will be permitted to access your records. There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study. A copy of this consent form will be kept in your medical record.

What are the costs of taking part in this study?

There are no costs involved in taking part in this study. 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 National Institutes of Health and National Institute of Child Health and Human Development are providing financial support and/or materials for this study.

What will happen if I am injured or become sick because I took part in this study?

No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study. If your child is injured or becomes sick as a result of this study, UNMHSC will provide him or her with emergency treatment, at your cost. It is important for you to tell your study doctor immediately if your child has been injured or becomes sick because of taking part in this study. If you have any questions about these issues, or believe that you have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, (505) 272-1129 for more information.

Will I be paid for taking part in this study?

No payment will be provided for this project.

How will I know if you learn something new that may change my mind about participating?

You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from participating in the research or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?

Your participation in this study is completely voluntary. You have the right to choose not to participate or to withdraw your participation at any point in this study without affecting your future health care or other services to which you are entitled.

At the discretion of the clinical provider, babies 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 or the study being canceled

Who can I call with questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Kristi Watterberg, M.D., or her associates will be glad to answer them at (505) 272-0180 on Monday through Friday between 9 am and 5 pm. If you would like to speak with someone other than the research team, you may call the UNMHSC HRRC at (505) 272-1129.

Who can I call with questions about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may call the UNMHSC HRRC at (505) 272-1129. The HRRC is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving human subjects. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/.

Consent

You are making a decision whether to have your child participate in this study. Your signature below indicates that you read the information provided (or the information was read to you). By signing this consent form, you are not waiving any of your child's legal rights as a research subject.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this consent form, I agree to participate or let my child participate in this study. A copy of this consent form will be provided to you.

_____
Name of Parent/Child's Legal Guardian

_____ _____
Signature of Parent/Child's Legal Guardian Date

I have explained the research to the subject and his/ her parent/legal representative, and answered all of his/ her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

_____	_____/ _____
Name of Investigator/ Research Team Member	Signature of Investigator/ Research Team Member Date

____Initials

OFFICIAL USE ONLY

APPROVED 9/1/2006 EXPIRES 8/14/2007

The University of New Mexico Human Research Review Committee 5-03470

From: Neil Finer
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Oximeter data
Date: Friday, September 15, 2006 3:45:20 PM
Attachments: Center 3 pct in range through Aug06 (supp O2).rtf

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Rose
Here is what a center report would look like. I think that we could send these to the individual centers. If we have a conference call organized for the subcommittee we could wait till then and ask the members to agree. If the call is going to be delayed, I would favor sending out site data.
Be well
Neil
-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 15, 2006 9:22 AM
To: Neil Finer
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Oximeter data

Great! Do you want to still hold off on sending the reports out?

Marie

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thu 9/14/2006 7:06 PM
To: Gantz, Marie
Subject: RE: Oximeter data

I Marie

This looks great.

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, September 14, 2006 1:06 PM
To: Neil Finer
Subject: RE: Oximeter data

Hi Neil,

I've attached an example center report. This report includes all 4 slices of oximeter data: before and after November, for DOL 1-14 and through 36 weeks. Let me know if you want me to make any changes (and let me know when you want the reports sent out).

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: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 07, 2006 12:52 PM
To: Gantz, Marie
Subject: RE: Oximeter data

Hi Marie

I think that we should send each unit their own data and the overall. For the units with too few infants/ hours or no enrollees, we should send them the overall data.

For now don't send anything while I compose an overall email and ask the SubCommittee to approve:

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, September 07, 2006 6:56 AM
To: Neil Finer
Subject: RE: Oximeter data

Hi Neil,

I just wanted to check in with you to see if there is any more action needed at this time from me. Do you want me to produce the center-specific reports?

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: Thursday, September 07, 2006 9:52 AM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Wally

I think that your targets are fine and 40-50% FOR THE 88-92 leaves some room. If you then look at what we have, the value for < 84 would be 10% - I would think that something even lower for < 84 may be appropriate, and were achieving that value if we don't consider the entire time on oxygen. Having these targets, and sending out reports to indicate the unit performance will be an incentive to improve performance.

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, September 07, 2006 3:46 AM
To: Neil Finer; Gantz, Marie

Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

I agree. While the 10% may be arbitrary, we should set some goals, and that one seems ok. Similarly, we should set a goal of 80% for the 84-96% range. The 80% comes from the German study. We should also set a goal for the 88-92%. I would not know where to suggest to put the goal but looking at the data, somewhere between 40-50% may be reasonable. I do not think these are easily accomplishable by each center every time but they may be able to do it on many babies.

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

Phone: (205) 934 4680

FAX: (205) 934 3100

Email: wcarlo@peds.uab.edu

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 06, 2006 10:03 PM
To: Gantz, Marie; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Marie, Wally, Rose, Ken and Abhik

This is very helpful. We seem to do better in the first 14 days and then we are less on target and more > 96% 16-18% versus 11% overall for all enrollments for the first 14 days from the beginning of the study. This value is identical for the infants enrolled since March for the first 14 days. Not all of these infants will be off of ventilators, but this may represent less precise control for infants on cannula/CPAP.

We may want to look at the mode of vent support and the SpO2 values to see if we pinpoint the areas that need further attention. I believe that out target > 96% should be 10%.

I think that I will arrange a conference call/web conference with the

Subcommittee before the Steering Comm.

Let me know if you agree.

Regards

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 06, 2006 2:51 PM
To: Neil Finer; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Neil,

Here are the new tables which include all time on supplemental oxygen through 36 weeks. The version of SUPP11 was not an issue after all - I missed the fact that the form was actually revised in March. Thus, for March through August, for day of life 15+, I determined oxygen use based on the nearest scheduled time at which oxygen use was recorded (6:00, 12:00, 18:00, or 23:59).

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: Wednesday, September 06, 2006 4:06 PM
To: Wally Carlo, M.D.; Gantz, Marie

Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data

Hi Marie and Wally.

The study is designed to keep the babies in range for all their time in oxygen. Thus I would use all the time available. For centers with enough data before June we could separate out prior to June as the first 14 days, and thereafter all oxygen days/hours. We do not know which times are more critical for the longer term, and I would not make any assumptions. I believe that the infants are coming off oxygen and support earlier and thus this should become less of an issue, but the mean time of ventilation for < 750gm was 20 days thus 14 days is not an appropriate limit.

Lets see what we have before we circulate and then I would have a teleconference to discuss before the Steering Comm meeting

Be well

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 06, 2006 8:43 AM
To: Gantz, Marie; Neil Finer
Subject: RE: Oximeter data

We should be careful so we do not compare apples and oranges. wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

Phone: (205) 934 4680

FAX: (205) 934 3100

Email: wcarlo@peds.uab.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 06, 2006 9:41 AM
To: Neil Finer
Cc: Wally Carlo, M.D.
Subject: RE: Oximeter data

Hi Neil,

So, am I interpreting you correctly to say that you want only data for days 1-14 up until June, but all days on supplemental oxygen for June-August?

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, September 05, 2006 4:39 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: RE: Oximeter data

Hi Marie

I would use all the available data after June, since these infants remain on study oximeters.

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, September 05, 2006 7:16 AM
To: Neil Finer
Subject: Oximeter data

Hi Neil,

I am working on preparing the tables of oximeter data you requested. I have one question, though - do you want me to include all study days, or only day of life 1-14? To include days 15+, SUPP11 would have to be used to determine time on supplemental oxygen. Previous to June, we only know if supplemental oxygen was used at any time during that day. Since June, we have supplemental oxygen recorded at 4 time points, so I would determine oxygen use at any given hour based on the information recorded at the closest time point. Let me know what you think.

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: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, September 01, 2006 9:39 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject:

Hi Marie

Could you also prepare a Table of data for infants enrolled before the November stoppage by site using the same ranges that we will use for the subsequent reports? This will allow the sites to evaluate whether they are improving the time in range and target.

As with the other data, please only prepare this for sites that had > 5 infants enrolled at that time, using time in Oxygen as being in oxygen for all 3 points that day. Thus there would be a row for each center with adequate infants and an overall row.

Please send this graph to me and Wally and Rose only, and we will then decide if this should have wider distribution.

Thanks

Neil

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH AUGUST 2006

TIME ON SUPPLEMENTAL 02 ONLY

(OXIMETER DATA PROCESSED AS OF 8/29/06)

Dates	Time on supplemental oxygen	Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Through Nov05	Days of life 1-14	3	1885.7	28.9	14.9	77.2	7.9
		All centers	25306.7	37.6	9.4	79.2	11.4
	Through 36 wks	3	18215.0	20.9	17.3	66.6	16.1
		All centers	158594.5	28.1	11.9	69.5	18.6
Mar06-Aug06	Days of life 1-14	3	1928.8	48.1	6.3	84.5	9.2
		All centers	9901.6	43.3	7.2	82.3	10.5
	Through 36 wks	3	9388.1	37.3	11.9	73.2	14.9
		All centers	40940.8	33.2	10.6	72.7	16.7

Center data not shown if the center had <=5 infants or <=1000 hours in the time period

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Cc: das@rti.org
Subject: RE: SUPPORT primary outcomes update
Date: Friday, September 15, 2006 3:39:26 PM

I agree
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 15, 2006 10:08 AM
To: Gantz, Marie; Neil Finer
Cc: das@rti.org
Subject: RE: SUPPORT primary outcomes update

If it is ok with Ahbik, I would like a list of patient numbers and center number with the missing ROP outcome. I can gently remind the PI's that we need to have this info for the first DSMC look at the data. WE really should have the data.

Thanks
ROSE

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 15, 2006 1:18 PM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: das@rti.org
Subject: SUPPORT primary outcomes update

Neil and Rose,

I received Neil's comments on the BPD definition, and will look at them more closely on Monday when I am back in the office (I am off-site attending a class today). However, I wanted to give you some idea of how close we are to the first interim analysis for SUPPORT. Using the attached definitions of BPD and ROP, we currently have final outcomes (survival without BPD/ROP) for 211 SUPPORT infants. We have about 75 additional infants who have known BPD but unknown ROP. The centers have been receiving monthly missing forms reports listing infants who have reached 50 weeks PMA but are missing ROP final status (last month there were 79 missing and this month there were 74). Almost all of these infants (67) have had at least one ROP exam, but final status has not been reached as defined in the SUPPORT MOP. It is possible that for some of these infants we will receive additional exam data, but only three have had exam data entered since April.

Obviously, if we had ROP outcomes on these infants we would be much closer to being able to do the first interim analysis of the data (which requires outcomes on 328 infants). So, I am wondering if you have any

ideas regarding how to treat these missing ROP outcomes. We have NG03 ROP data on most of the infants, but for all but a couple, it is data from the 2002 version of the form. We might be able to make some ROP determinations using this data if the ROP criteria from the new NG03 are applied, but they are slightly different from those listed in the SUPPORT MOP. Even if we do use the NG03 data, it looks like 50-60 infants will fall into the undetermined category.

Please let me know if you have any thoughts on this issue.

Thanks,

Marie

Marie Gantz, Ph.D.

Research Statistician

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mgantz@rti.org

From: Gantz, Marie
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: das@rti.org
Subject: SUPPORT primary outcomes update
Date: Friday, September 15, 2006 1:21:55 PM
Attachments: ROP def for SUPPORT 9-12-06.doc
Flow Chart - Phys Def SUPPORT 9-12-06.doc

Neil and Rose,

I received Neil's comments on the BPD definition, and will look at them more closely on Monday when I am back in the office (I am off-site attending a class today). However, I wanted to give you some idea of how close we are to the first interim analysis for SUPPORT. Using the attached definitions of BPD and ROP, we currently have final outcomes (survival without BPD/ROP) for 211 SUPPORT infants. We have about 75 additional infants who have known BPD but unknown ROP. The centers have been receiving monthly missing forms reports listing infants who have reached 50 weeks PMA but are missing ROP final status (last month there were 79 missing and this month there were 74). Almost all of these infants (67) have had at least one ROP exam, but final status has not been reached as defined in the SUPPORT MOP. It is possible that for some of these infants we will receive additional exam data, but only three have had exam data entered since April.

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Criteria for Determining ROP Status for SUPPORT

9/12/2006

The SUPPORT MOP criteria for attaining ROP acute/final status (favorable or unfavorable) are listed below. For the purpose of determining the SUPPORT primary outcomes, I am assuming that both eyes need to reach acute/final status, and that status is met when any *one* of the criteria below is met. The sub-bullets in blue describe the way I would determine the criteria using fields from the SUPP10.

Favorable (Primary Outcome = No ROP)

- Vessel growth if mature to the ora serrata in all clock hours
  - Lowest Zone of any Vessels = 4 (Mature)
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)
  - Lowest Zone of any Vessels = 3 (III) for two consecutive exams

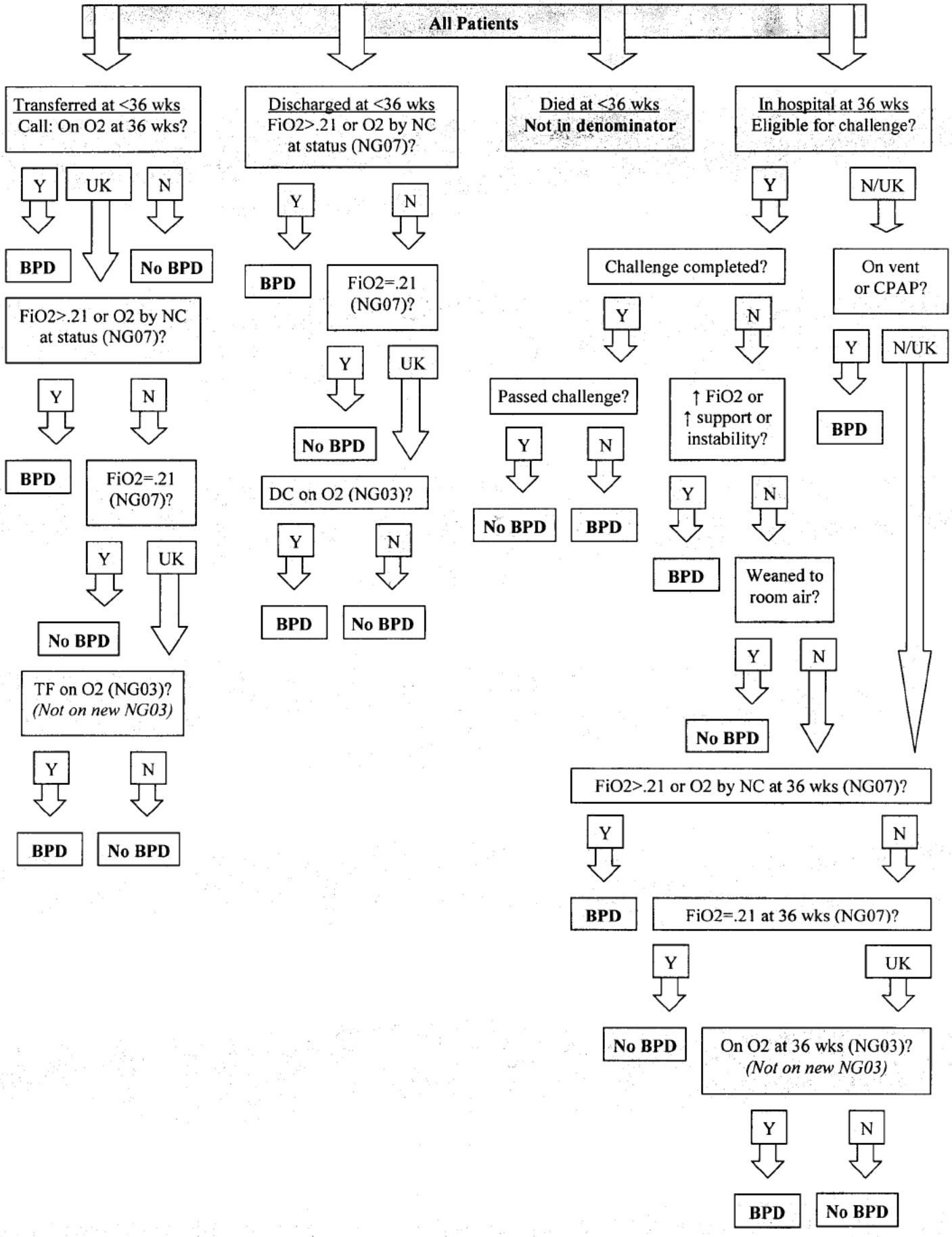
Unfavorable (Primary Outcome = ROP)

- Type I threshold ROP
  - Threshold (New Type 1) = Y
- Laser (or cryo or both) surgery for acute ROP
  - Surgery = 1 (Laser) or 2 (Cryotherapy) or 3 (Both laser/cryo) or 4 (Scleral buckle) or 5 (Vitrectomy) or 6 (Other) *NOTE: the protocol lists "need for surgery" as severe ROP, without specifying laser or cryotherapy. Should the other types of surgery be included as well?*
  - Post-surgical Retinal Detachment = 3 (Stage 4a) or 4 (Stage 4b) or 5 (Complete) or 9 (View obscured, can't tell)
  - Lowest Zone of any Vessels = 5 (Status post laser/cryo)
  - Highest Stage in any Zone = 6 (Post laser/cryo)
- Retinal detachment stage 5
  - Highest Stage in any Zone = 5 (Stage 5)
- Retinal detachment stage 4b
  - Highest Stage in any Zone = 4 (Stage 4a or 4b) *NOTE: 4a and 4b cannot be separated because of the way they are coded on SUPP10.*

Other

- Infant dies

PHYSIOLOGIC DEFINITION OF BPD FOR INFANTS IN SUPPORT TRIAL



5-03486

PHYSIOLOGIC DEFINITION OF BPD FOR INFANTS IN SUPPORT TRIAL

Assumptions made in BPD flow chart:

1. If an infant is transferred prior to 36 weeks and information regarding whether the infant was on room air at 36 weeks is not available from the receiving hospital, BPD determination should be made based on NG07 data, if available, followed by NG03 data. *Note: transferred on oxygen variable is not on the new version of the NG03.*
2. If an infant is discharged prior to 36 weeks, BPD determination should be made based on NG07 data, if available, followed by NG03 data.
3. If an infant is not eligible for the physiologic evaluation because the answer to a, b, and c below (from form PHY01) are all No, it cannot be assumed that the infant has BPD. A determination must be made based on data from NG07 or NG03. *Note: supplemental oxygen at 36 weeks is not on the new version of the NG03.*
    a. Effective oxygen <27% AND majority saturation ≥90%
    b. Effective oxygen 27-30% AND majority saturation ≥96%
    c. Room air by nasal cannula
4. If an infant is on room air by nasal cannula at 36 weeks and is challenged, the outcome of the challenge will be used to determine BPD status.

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer
Subject: Oximeters
Date: Wednesday, September 13, 2006 5:28:08 PM

Rose,

I have left you out of this email loop because it was lengthy. Here is some news re: oximeters:

Problem 1: Version 5 oximeters, i.e. those purchased AFTER the DSMC meeting and from here on, are not compatible with the RTI analysis software. The exception to this is the 10 UAB purchased, which have had old boards put in them so that functionally they are back to being Version 4 oximeters. Any new oximeters purchased for the trial will be a problem.

Problem 2: A group of oximeters has shown up with the "stock" histogram that comes with off-the-shelf Masimos. Kris from RTI has Fed-Ex'd me one of them so that I can test it with a simulator to see if it is a skewed SUPPORT oximeter or not. If not, a hunk of Miami's data may be of little value. I will keep you apprised of the situation.

Wade

From: Neil Finer
To: Walsh, Michele; Gantz, Marie
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Wednesday, September 13, 2006 12:50:50 PM

Hi Michelle
These are interesting observations. After 14 days we decided that we only collect Oxygen. Yes/no, not the actual FiO2 so that such calculations cannot be made from our forms. Infants on CPAP and room air are coded as CPAP and room air, these are indicated. One thought is to use a high alarm in room air – such as 99% - we are now using this for the first few days out of oxygen as part of our QI to improve SpO2 targets. We would count all infants in Oxygen, any level as being in O2 and you may be correct that the effective FiO2 may be 21%. Are you seeing infants on cannula with low FiO2 settings with SpO2 > 95%? This would be dealt with by the caretakers who would presumably lower the flow or FiO2. Or, in your unit, is their an understanding that low cannula flows with low FiO2 are equivalent to room air, and your care teams are defeating the high alarm?
Let me know
Wade can now take a breath!!!!!
Be well
Neil

From: Walsh, Michele [mailto:Michele.Walsh@uhhs.com]
Sent: Wednesday, September 13, 2006 6:49 AM
To: Neil Finer; Gantz, Marie
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

I have noticed a tendency at our site- to have kids in RA cpap with very high sats,
(generally for apnea) and people forget that they could wean the pressure to reduce the sat.
I am trying to figure out if this is a component of the high sats at >14 days.
Do we have a way to figure this out?
Also: could be as we saw in the Phys Def study that people do not routinely account for
effective FiO2 when infants are in nasal cannula. This leads to meny kids (50% of the cohort in Phys Def) who are effectively in RA in nc, but are counted as "in oxygen" by our analysis. Could calculating the effective FiO2 improve our classification of a child? We could either do this clinically, by having the research nurses calculate effective FiO2- perhaps prompting removal of the nc by the clinical team (OK: Wade- I suspect you are gasping!),
or on a study basis at RTI to remove them from the analysis?
Best, Michele

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tue 9/12/2006 5:15 PM
To: Walsh, Michele; Gantz, Marie
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Michelle

To our knowledge, Marie looked at FiO2, irrespective of any other support.
Marie, can you confirm this?? Or not!!
Neil

From: Walsh, Michele [mailto:Michele.Walsh@uhhs.com]

Sent: Tuesday, September 12, 2006 1:20 PM
To: Neil Finer
Subject: RE: Oximeter data for the SUPPORT Trial

Neil: I was looking at our data more carefully. Do the days include those with support (eg CPAP) but roomair? Michele

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 07, 2006 1:13 PM
To: Neil Finer; Wally Carlo, M.D.; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; higginsr@mail.nih.gov
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
I wanted to send some data to the sites regarding the Oximeter study within SUPPORT. We have now received from Marie at RTI information about the iverall SpO2 values, which remain blinded: that is both hi and lo oximeter data is combined, and the data is the non-converted values, those that show on the actual oximeter at the bedside. Up until now we have only used information from the first 14 days in oxygen. Before March we had defined in oxygen as a day during which all 3 time points for which we collected data were in oxygen. Since March we have used the new forms which allow information every 2 hours about oxygen.
I propose that all sites receive the overall data as I have listed it below

All Centers	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96

Data prior to Stoppage Nov 2005:

All centers	**158594.5**	**28.1**	**11.9**	**69.5**	**18.6**

From March to August 2006:

All centers	**40940.8**	**33.2**	**10.6**	**72.7**	**16.7**

From this information and comparing this to the data for only the first 14 days, we do better in the first 14 days with respect to keeping the infants < 96% and in the narrow target.
I think that we need to show the overall data as the infants spend a great deal of time on oxygen off of ventilators and CPAP, and our hypothesis is that controlling their SpO2 all the time, not just when on vents etc, will improve outcomes.
We can also send them the data for the first 14 days which may be confusing. This is what that data looks like:

Data prior to Nov Stoppage first 14 days in O2

All centers	**25306.7**	**37.6**	**9.4**	**79.2**	**11.4**

Data from March 2006 for first 14 days

All centers	**9901.6**	**43.3**	**7.2**	**82.3**	**10.5**

Please take a few minutes to look at this. I would also send each site its own data, but not circulate individual site data to other sites.
I have attached another file with this information in case via email the spacing etc gets scrambled. In

addition I have sent you the original files from Marie.
Have fun and thanks to Marie!!
Neil

CELEBRATING 140 YEARS of Caring for Cleveland.

The enclosed information is STRICTLY CONFIDENTIAL and is intended for the use of the addressee only. University Hospitals Health System and its affiliates disclaim any responsibility for unauthorized disclosure of this information to anyone other than the addressee.

Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR 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.

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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: protocol deviation
Date: Wednesday, September 13, 2006 12:39:55 PM

Hi Rose
I would just want to indicate that even if the IRB at Houston is OK with this, I would have a mild worry that if this child has problems, there may be later concerns that the initial therapy and subsequent consent may be a risk factor.
I would suggest that Houston also pass through their risk management group.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 13, 2006 6:05 AM
To: Das, Abhik; Tyson, Jon E; Mcdavid, Georgia E; Petrie, Carolyn; Zaterka-Baxter, Kristin
Cc: Morris, Brenda H; Poole, W. Kenneth; Gantz, Marie; Neil Finer
Subject: RE: protocol deviation

This is fine and I confirmed with Georgia and Patty that their IRB had been informed.

Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, September 13, 2006 8:59 AM
To: Tyson, Jon E; Mcdavid, Georgia E; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Zaterka-Baxter, Kristin
Cc: Morris, Brenda H; Poole, W. Kenneth; Gantz, Marie; nfiner@ucsd.edu
Subject: RE: protocol deviation

I think we can, since we have her consent on file. Georgia can enter a protocol deviation record because the subject was randomized before consent was obtained.

Thanks

Abhik

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Tuesday, September 12, 2006 7:05 PM
To: Das, Abhik; Mcdavid, Georgia E; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Zaterka-Baxter, Kristin
Cc: Morris, Brenda H
Subject: RE: protocol deviation

Good for Brenda. Will RTI include in the 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: Mcdavid, Georgia E
Sent: Tuesday, September 12, 2006 2:39 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'
Cc: Morris, Brenda H; Tyson, Jon E
Subject: protocol deviation

FYI: On [redacted] infant (b) (6) was randomized in error to the SUPPORT study. The error was made in the delivery room by the respiratory therapist. We make a list of mothers that have consented for the study and update the list every working day. This list is kept in the doctors lounge, the transport nurses office and in the Respiratory Therapist area. Also, in a separate area on the list we document those mothers that have refused the study so that our doctors will not try and consent a mother we have already approached. This area is shaded to further differentiate it from "consented" list. The lists are available to all delivery room personnel. The Respiratory Therapist (RT) that is primarily responsible for randomizing and starting the randomized treatment. In this case the RT had made a copy of the list and was not clear about the differentiation the between consented and refused lists. This mother was listed under the "refused" area of the page. They saw the name on the list and assumed they were consented and randomized the infant. The infant was randomized to intubation and early surfactant. When the error was discovered the next morning Dr. Morris went to speak to the mother. After explaining what happened, the mother was willing to sign the consent.

To avoid the same problem in the future all shading has been removed from the page and the refusal has very little information, other than the last date the infant is eligible. All responsible parties have been re-inserviced on the paper.

From: Walsh, Michele
To: Wally Carlo, M.D.; Neil Finer; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Saturday, September 09, 2006 8:35:18 AM

Neil; I think this data will be very helpful. I would advocate for sharing both the first 14 day data, and the total date. In my opinion, one of the lessons of the benchmark trial is that focusing on the first 14 days only (when most of the bench interventions applied) wll do little to change BPD. We need to focus on the entire care and remain vigilant about oxygen exposure as they are convalescent- esp while in nasal canula.
Thanks for keeping on top of this complex data set- over 159,000 hours of data- whoa!
Michele

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Fri 9/8/2006 6:11 PM
To: Neil Finer; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; higginsr@mail.nih.gov
Subject: RE: Oximeter data for the SUPPORT Trial

Neil:

Great idea! I think this will be helpful and allow the investigators to aim for better compliance.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Neil Finer [mailto:nfiner@ucsd.edu]
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To: Neil Finer; Wally Carlo, M.D.; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; higginsr@mail.nih.gov
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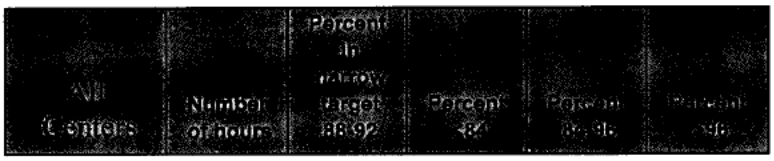

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I have attached another file with this information in case via email the spacing etc gets scrambled. In addition I have sent you the original files from Marie.
Have fun and thanks to Marie!!
Neil

From: Wally Carlo, M.D.
To: Neil Finer; Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Thursday, September 07, 2006 7:09:35 PM

Brad:

We use the NeoTech long prongs and have used the 2.5 in 400 gram babies.
On smaller babies, we have use an oropharyngeal tube for CPAP.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 07, 2006 3:51 PM
To: Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; Wally Carlo, M.D.; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc: higginsr@mail.nih.gov; Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hi Brad
Our experience is that the size O starts getting too small about 700g or so and the resistance in the Argyles is very high. We use the Fisher & Paykel prongs for some of these kids, and on rare occasions, the Argyles. The other option is to use size 3 Hudson prongs in a Viasys nasal mask. This has also worked well for us for some infants.
I have sent some pictures of how these mate. This is not a recommended application, but has worked for us for a number of infants.
Hope that this helps
Neil
-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Thursday, September 07, 2006 9:49 AM
To: mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; Neil Finer; ALaptook@wihri.org
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

We have had some problems over the past week with getting "O" sized Hudson nasal prongs into the nares of babies < 700 grams.
Has that been an issue for any of you? If so, how have you dealt with it?

Has anyone been using the Argyle CPAP nasal prongs? The outer diameter is smaller, but so is the internal diameter.

Thanks.

Brad Yoder

>>> "Neil Finer" <nfiner@ucsd.edu> 8/24/2006 10:44:46 AM >>>

Hello Everyone
I am attaching information about the oximeter data using all available baby data for time in oxygen since the trial began. It includes the infant enrolled prior to the stoppage for which we used in oxygen at all 3 time points in a day and the infants subsequently enrolled for whom we use the 2 hourly data to determine if they are in oxygen.
Do you think that we should send this information to all centers, only those that have enrolled, or none at this time?
Thanks for your input.
Regards
Neil

From: Wade Rich
To: Neil Finer; Bradley Yoder
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Thursday, September 07, 2006 6:19:22 PM

Just keep those Antenatal Consent study forms coming !!
wade

-----Original Message-----
From: Neil Finer
Sent: Thursday, September 07, 2006 3:12 PM
To: 'Bradley Yoder'
Cc: Wade Rich; 'higginsr@mail.nih.gov'
Subject: RE: Oximeter data for the SUPPORT Trial

Hi Brad
Glad to hear that this worked. As we said, the best tocolytic ever invented is the SUPPORT Consent.
Be well
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Thursday, September 07, 2006 2:58 PM
To: Neil Finer
Subject: RE: Oximeter data for the SUPPORT Trial

Thanks Neil.
I had them adapt the XS-Argyle prongs to the bubble CPAP system and it fit very nicely & the infant seems quite comfrotable.
If you look at the Study by DePaoli from 2002 where they did in vitro comparison of several different CPAP interfaces, there doesn't appeara to be much difference between the Hudson 0 and the XS-Argyle, though both have are quite different than the large bore prongs of the same make.
This may be due to the very short length of the Argyle relative to the Hudson.

Michele says that they had some masks made for this use & will send me the info.
I'll forward it to you if it is different than the Vivasys/IFD mask.

We have several mothers consented for the SUPPORT at the U & LDS. But every one of them has decided to "maintain" their pregnancy. The only deliveries we are having in the defined gestational age group are those who have refused or in whom we haven't been able to communicate with to get consent. Is a tocolytic trial on the horizon??

Thanks for your response.

Brad

>>> "Neil Finer" <nfiner@ucsd.edu> 9/7/2006 3:50:53 PM >>>
Hi Brad

Our experience is that the size O starts getting too small about 700g or so and the resistance in the Argyles is very high. We use the Fisher & Paykel prongs for some of these kids, and on rare occasions, the Argyles. The other option is to use size 3 Hudson prongs in a Viasys nasal mask. This has also worked well for us for some infants.
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Hope that this helps
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From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Thursday, September 07, 2006 9:49 AM
To: mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; Neil Finer; ALaptook@wihri.org
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Has that been an issue for any of you? If so, how have you dealt with it?
Has anyone been using the Argyle CPAP nasal prongs? The outer diameter is smaller, but so is the internal diameter.

Thanks.

Brad Yoder

>>> "Neil Finer" <nfiner@ucsd.edu> 8/24/2006 10:44:46 AM >>>

Hello Everyone
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Do you think that we should send this information to all centers, only those that have enrolled, or none at this time?
Thanks for your input.
Regards
Neil

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Thursday, September 07, 2006 5:12:50 PM

I forwarded the request to Robin

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 07, 2006 4:55 PM
To: Petrie, Carolyn
Subject: FW: Oximeter data for the SUPPORT Trial

Can you schedule a call for SUPPORT??
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 07, 2006 1:13 PM
To: Neil Finer; Wally Carlo, M.D.; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
I wanted to send some data to the sites regarding the Oximeter study within SUPPORT. We have now received from Marie at RTI information about the iverall SpO2 values, which remain blinded: that is both hi and lo oximeter data is combined, and the data is the non-converted values, those that show on the actual oximeter at the bedside. Up until now we have only used information from the first 14 days in oxygen. Before March we had defined in oxygen as a day during which all 3 time points for which we collected data were in oxygen. Since March we have used the new forms which allow information every 2 hours about oxygen.
I propose that all sites receive the overall data as I have listed it below

All Centers	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
Data prior to Stoppage Nov 2005:					
All centers	158594.5	28.1	11.9	69.5	18.6
From March to August 2006:					
All centers	40940.8	33.2	10.6	72.7	16.7

From this information and comparing this to the data for only the first 14 days, we do better in the first 14 days with respect to keeping the infants < 96% and in the narrow target.
I think that we need to show the overall data as the infants spend a great deal of time on oxygen off of ventilators and CPAP, and our hypothesis is that controlling their SpO2 all the time, not just when on vents etc, will improve outcomes.
We can also send them the data for the first 14 days which may be confusing. This is what that data looks like:

Data prior to Nov Stoppage first 14 days in O2					
All centers	25306.7	37.6	9.4	79.2	11.4

Data from March 2006 for first 14 days

All centers	**9901.6**	**43.3**	**7.2**	**82.3**	**10.5**

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Neil

From:	Neil Finer
To:	Bradley Yoder; mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; ALaptook@wihri.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Thursday, September 07, 2006 4:50:33 PM
Attachments:	DSCF0048.JPG DSCF0050.JPG DSCF0053.JPG

Hi Brad
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To: mcw3@case.edu; nxs5@case.edu; kurt.schibler@cchmc.org; Roger Faix; higginsr@mail.nih.gov; WCarlo@peds.uab.edu; adas@rti.org; mgantz@rti.org; poo@rti.org; Neil Finer; ALaptook@wihri.org
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Subject: RE: Oximeter data for the SUPPORT Trial

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>>> "Neil Finer" <nfiner@ucsd.edu> 8/24/2006 10:44:46 AM >>>

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those that have enrolled, or none at this time?
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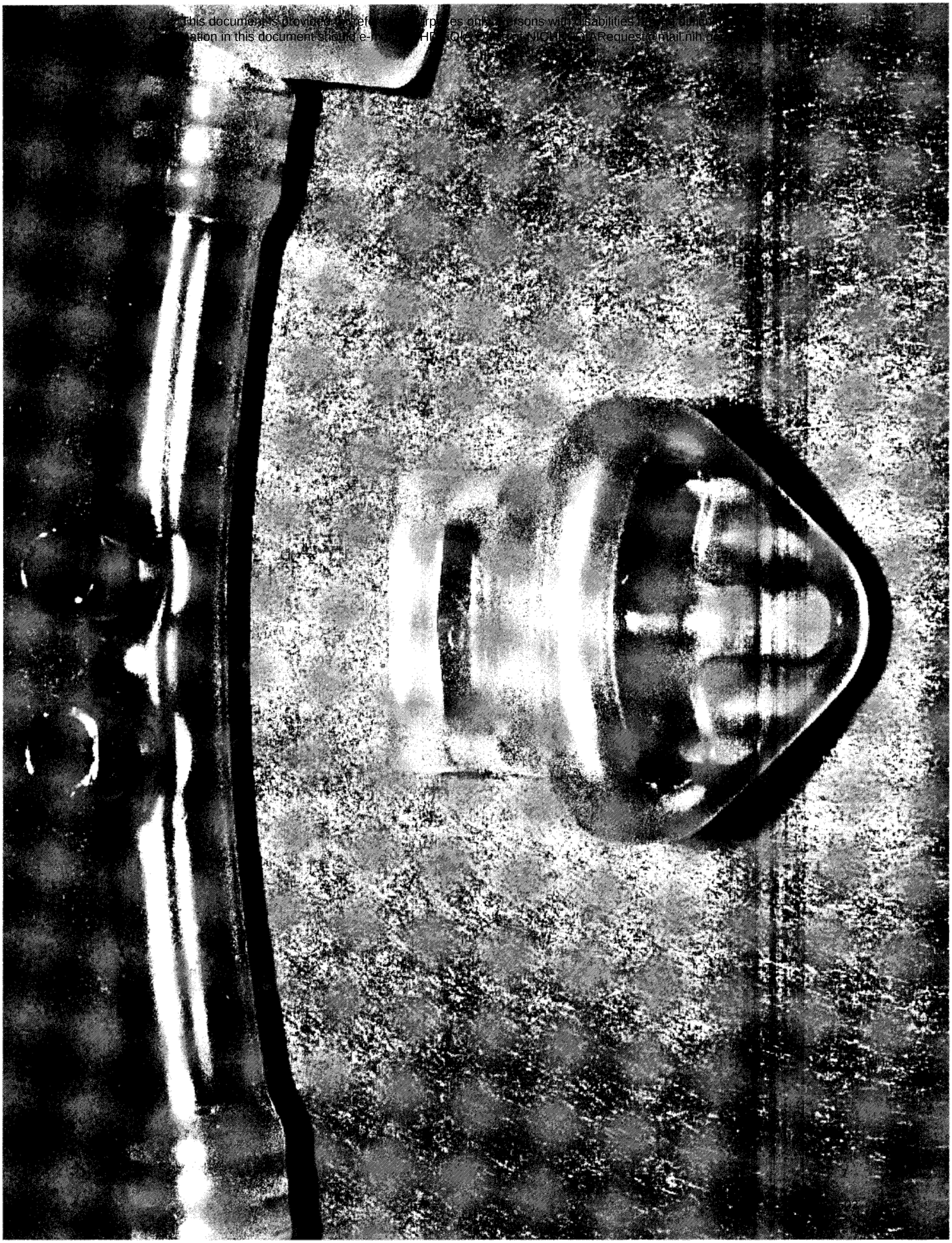
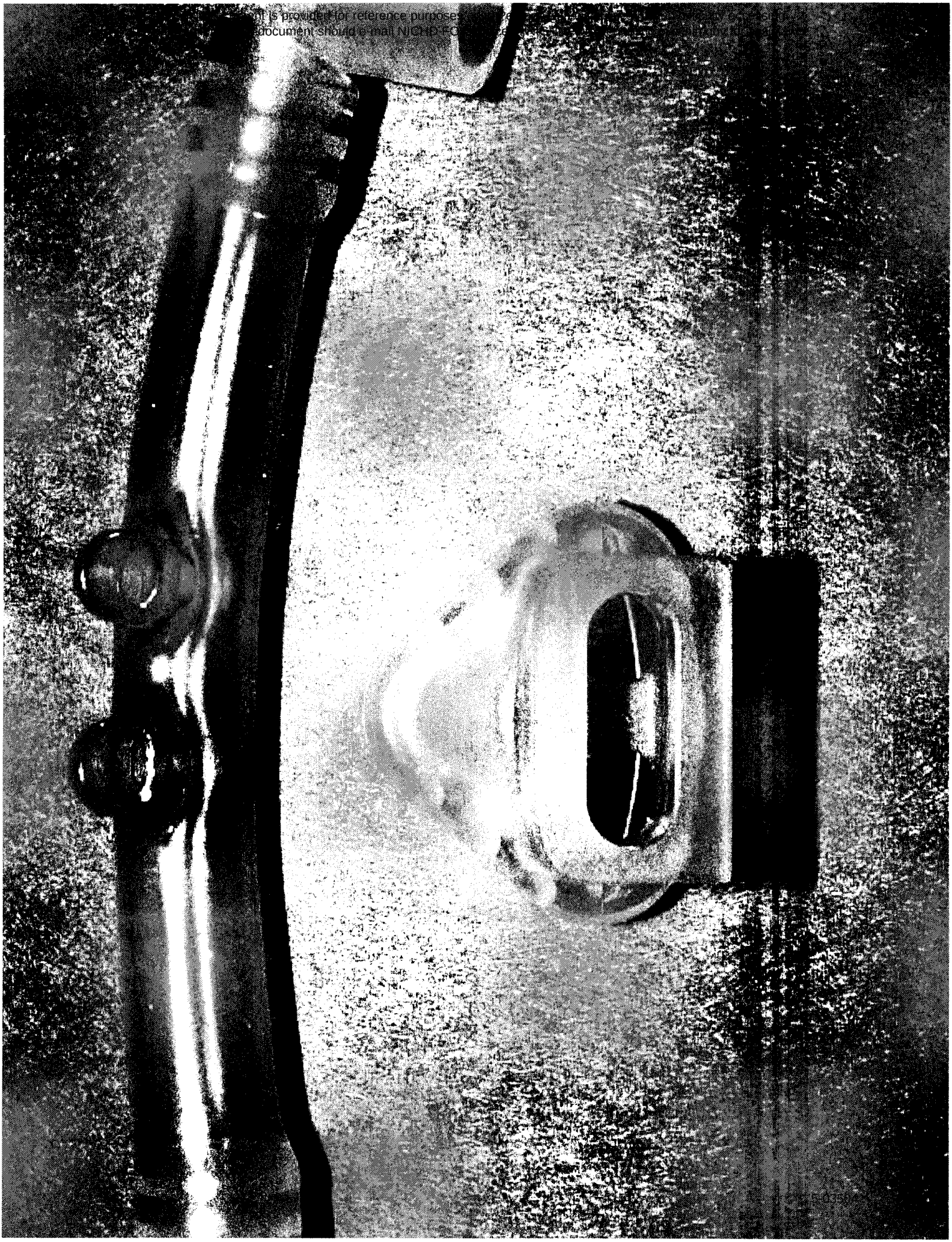
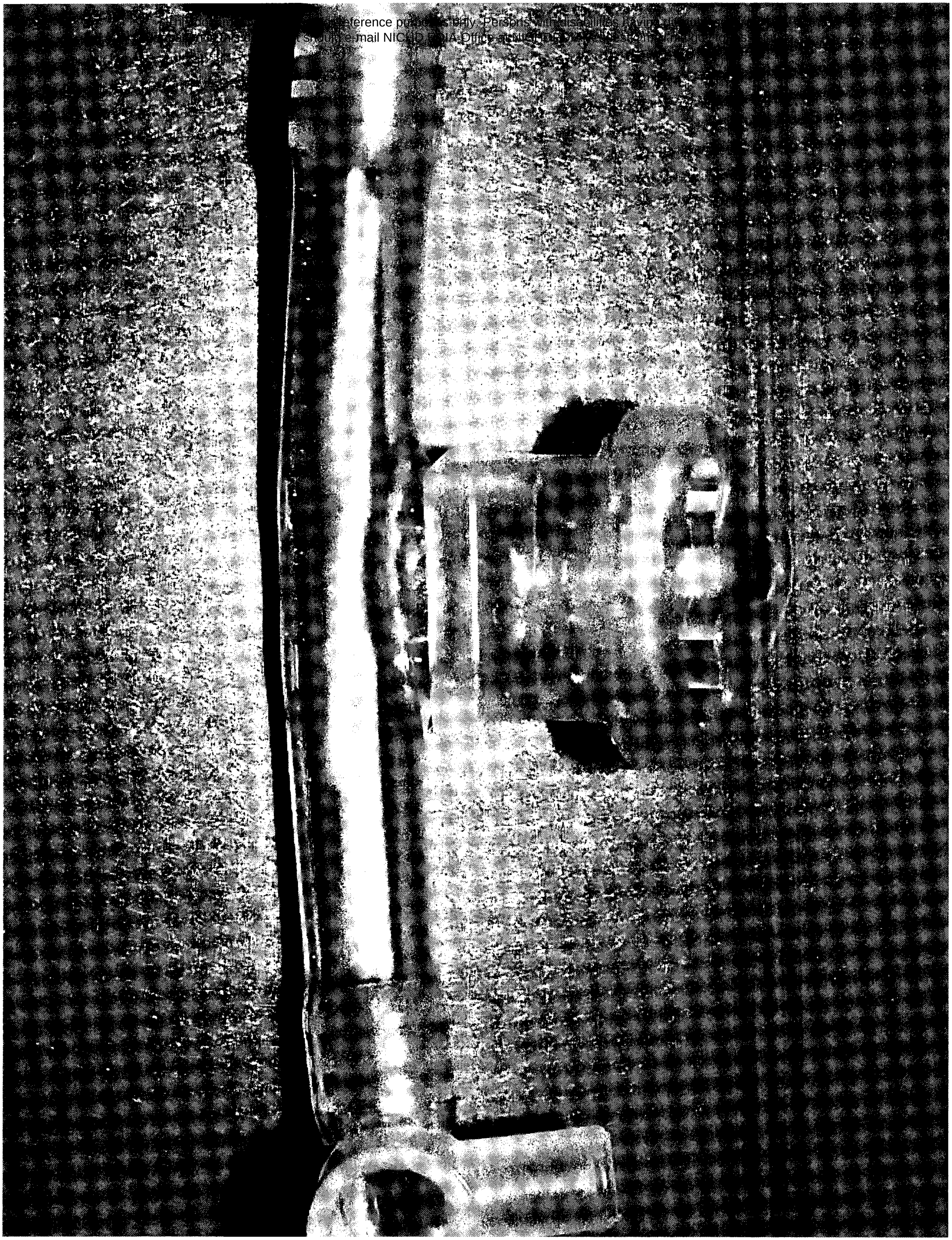
Regards
Neil







From: Neil Finer
To: Neil Finer; Wally Carlo, M.D.; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Thursday, September 07, 2006 1:12:28 PM
Attachments: Oximeter overall data Sept 2006.doc
Centers pct in range Mar06-Aug06 (supp O2 all days).rtf
Centers pct in range Mar06-Aug06 (supp O2) 14 days.rtf
Centers pct in range through Nov05 (supp O2 all days).rtf
Centers pct in range through Nov05 (supp O2)14 days.rtf

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All centers	**158594.5**	**28.1**	**11.9**	**69.5**	**18.6**

From March to August 2006:

All centers	**40940.8**	**33.2**	**10.6**	**72.7**	**16.7**

From this information and comparing this to the data for only the first 14 days, we do better in the first 14 days with respect to keeping the infants < 96% and in the narrow target.
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We can also send them the data for the first 14 days which may be confusing. This is what that data looks like:

Data prior to Nov Stoppage first 14 days in O2

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Data from March 2006 for first 14 days

All centers	**9901.6**	**43.3**	**7.2**	**82.3**	**10.5**

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I propose that all sites receive the overall data as I have listed it below

All Centers	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96

Data prior to Stoppage Nov 2005: all time on O2

All centers	158594.5	28.1	11.9	69.5	18.6

From March to August 2006:all time in O2

All centers	40940.8	33.2	10.6	72.7	16.7

From this information and comparing this to the data for only the first 14 days, we do better in the first 14 days with respect to keeping the infants < 96% and in the narrow target.
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Thanks
Neil

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES MARCH 2006-AUGUST 2006

HOURS ON SUPPLEMENTAL 02 ONLY (THROUGH 36 WEEKS)

(DATA PROCESSED AS OF 8/29/06)

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	9388.1	37.3	11.9	73.2	14.9
9	4618.5	36.8	10.1	72.8	17.2
12	7964.0	25.4	10.7	72.6	16.7
14	8630.7	33.0	11.2	73.5	15.2
16	6375.7	42.1	8.9	75.4	15.7
All centers	**40940.8**	**33.2**	**10.6**	**72.7**	**16.7**

Center data not shown for centers with <=5 infants or <=1000 hours between March 2006 and August 2006

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES MARCH 2006-AUGUST 2006

DAY OF LIFE 1-14, HOURS ON SUPPLEMENTAL 02 ONLY

(DATA PROCESSED AS OF 8/29/06)

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	1928.8	48.1	6.3	84.5	9.2
12	1529.4	36.3	7.3	83.0	9.7
14	2095.0	41.7	8.2	82.9	8.9
16	2668.2	49.8	5.8	85.2	9.0
All centers	**9901.6**	**43.3**	**7.2**	**82.3**	**10.5**

Center data not shown for centers with <=5 infants or <=1000 hours between March 2006 and August 2006

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH NOVEMBER 2005

DAYS ON SUPPLEMENTAL O2 ONLY (THROUGH 36 WEEKS)

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	18215.0	20.9	17.3	66.6	16.1
4	6092.6	21.7	7.4	66.2	26.5
8	6259.6	20.2	8.1	61.6	30.3
9	12496.9	31.7	12.6	69.6	17.7
11	12155.4	29.0	10.1	68.4	21.4
12	10451.2	35.0	9.4	74.0	16.6
14	22284.3	27.3	11.4	72.2	16.5
16	21260.2	33.1	11.7	73.7	14.6
18	13146.6	26.9	16.5	67.6	16.0
20	10806.6	22.3	11.0	65.3	23.7
22	21156.2	31.4	9.9	69.3	20.8
All centers	**158594.5**	**28.1**	**11.9**	**69.5**	**18.6**

Center data not shown for centers with <=5 infants or <=1000 hours through November 2005

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH NOVEMBER 2005

DAY OF LIFE 1-14, DAYS ON SUPPLEMENTAL 02 ONLY

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	1885.7	28.9	14.9	77.2	7.9
8	1447.8	29.6	6.6	73.3	20.1
9	1985.3	38.9	11.8	77.5	10.7
11	1946.7	36.9	9.3	75.6	15.1
12	1341.5	45.9	6.7	80.8	12.4
14	3171.0	38.4	8.8	83.1	8.1
16	5498.1	42.5	9.5	81.4	9.2
18	1509.4	31.2	10.2	77.0	12.9
20	1860.4	30.8	7.5	74.1	18.4
22	3322.5	40.1	8.6	79.5	11.9
All centers	**25306.7**	**37.6**	**9.4**	**79.2**	**11.4**

Center data not shown for centers with <=5 infants or <=1000 hours through November 2005

From: Wally Carlo, M.D.
To: Neil Finer; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data
Date: Thursday, September 07, 2006 10:05:52 AM

Hi Neil: I agree. wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 07, 2006 8:52 AM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Wally
I think that your targets are fine and 40-50% FOR THE 88-92 leaves some room. If you then look at what we have, the value for < 84 would be 10% - I would think that something even lower for < 84 may be appropriate, and were achieving that value if we don't consider the entire time on oxygen. Having these targets, and sending out reports to indicate the unit performance will be an incentive to improve performance.
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, September 07, 2006 3:46 AM
To: Neil Finer; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

I agree. While the 10% may be arbitrary, we should set some goals, and that one seems ok. Similarly, we should set a goal of 80% for the 84-96% range. The 80% comes from the German study. We should also set a goal for the 88-92%. I would not know where to suggest to put the goal but looking at the data, somewhere between 40-50% may be reasonable. I do not think these are easily accomplishable by each center every time but they may be able to do it on many babies.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 06, 2006 10:03 PM
To: Gantz, Marie; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Marie, Wally, Rose, Ken and Abhik
This is very helpful. We seem to do better in the first 14 days and then we are less on target and more > 96% 16-18% versus 11% overall for all enrollments for the first 14 days from the beginning of the study. This value is identical for the infants enrolled since March for the first 14 days. Not all of these infants will be off of ventilators, but this may represent less precise control for infants on cannula/CPAP.
We may want to look at the mode of vent support and the SpO2 values to see if we pinpoint the areas that need further attention. I believe that out target > 96% should be 10%.
I think that I will arrange a conference call/web conference with the Subcommittee before the Steering Comm.
Let me know if you agree.
Regards
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 06, 2006 2:51 PM
To: Neil Finer; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data

Hi Neil,

Here are the new tables which include all time on supplemental oxygen through 36 weeks. The version of SUPP11 was not an issue after all – I missed the fact that the form was actually revised in March. Thus, for March through August, for day of life 15+, I determined oxygen use based on the nearest scheduled time at which oxygen use was recorded (6:00, 12:00, 18:00, or 23:59).

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: Wednesday, September 06, 2006 4:06 PM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data

Hi Marie and Wally.
The study is designed to keep the babies in range for all their time in oxygen. Thus I would use all the time available. For centers with enough data before June we could separate out prior to June as the first 14 days, and thereafter all oxygen days/hours. We do not know which times are more critical for the longer term, and I would not make any assumptions. I believe that the infants are coming off oxygen and support earlier and thus this should become less of an issue, but the mean time of ventilation for < 750gm was 20 days thus 14 days is not an appropriate

limit.
Lets see what we have before we circulate and then I would have a teleconference to discuss before the Steering Comm meeting
Be well
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 06, 2006 8:43 AM
To: Gantz, Marie; Neil Finer
Subject: RE: Oximeter data

We should be careful so we do not compare apples and oranges. wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 06, 2006 9:41 AM
To: Neil Finer
Cc: Wally Carlo, M.D.
Subject: RE: Oximeter data

Hi Neil,

So, am I interpreting you correctly to say that you want only data for days 1-14 up until June, but all days on supplemental oxygen for June-August?

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, September 05, 2006 4:39 PM
To: Gantz, Marie
Cc: Wally Carlo, M.D.
Subject: RE: Oximeter data

Hi Marie
I would use all the available data after June, since these infants remain on study oximeters.

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, September 05, 2006 7:16 AM
To: Neil Finer
Subject: Oximeter data

Hi Neil,

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Thanks,
Marie

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Sent: Friday, September 01, 2006 9:39 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject:

Hi Marie
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Thanks
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From: Neil Finer
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data
Date: Wednesday, September 06, 2006 7:26:05 PM

Hi Marie
That would be great – but I would still want an overall as well.
Thanks
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, September 06, 2006 1:14 PM
To: Neil Finer; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data

Thanks for the clarification, Neil – I was a little confused, but now I understand what you're saying. Do you want me to see if there is enough data to separate out the first 14 days?

Marie

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Research Statistician
RTI International
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Telephone (919) 485-7780
Fax (919) 485-7762
mgantz@rti.org

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 06, 2006 4:06 PM
To: Wally Carlo, M.D.; Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data

Hi Marie and Wally.
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Thanks
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From: Gantz, Marie
To: Neil Finer; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth
Subject: RE: Oximeter data
Date: Wednesday, September 06, 2006 6:51:16 PM
Attachments: Centers pct in range through Nov05 (supp O2 all days).rtf
Centers pct in range Mar06-Aug06 (supp O2 all days).rtf

Hi Neil,

Here are the new tables which include all time on supplemental oxygen through 36 weeks. The version of SUPP11 was not an issue after all – I missed the fact that the form was actually revised in March. Thus, for March through August, for day of life 15+, I determined oxygen use based on the nearest scheduled time at which oxygen use was recorded (6:00, 12:00, 18:00, or 23:59).

Marie

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-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, September 01, 2006 9:39 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Subject:

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Please send this graph to me and Wally and Rose only, and we will then decide if this should have wider distribution.
Thanks
Neil

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES THROUGH NOVEMBER 2005
DAYS ON SUPPLEMENTAL 02 ONLY (THROUGH 36 WEEKS)

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	18215.0	20.9	17.3	66.6	16.1
4	6092.6	21.7	7.4	66.2	26.5
8	6259.6	20.2	8.1	61.6	30.3
9	12496.9	31.7	12.6	69.6	17.7
11	12155.4	29.0	10.1	68.4	21.4
12	10451.2	35.0	9.4	74.0	16.6
14	22284.3	27.3	11.4	72.2	16.5
16	21260.2	33.1	11.7	73.7	14.6
18	13146.6	26.9	16.5	67.6	16.0
20	10806.6	22.3	11.0	65.3	23.7
22	21156.2	31.4	9.9	69.3	20.8
All centers	**158594.5**	**28.1**	**11.9**	**69.5**	**18.6**

Center data not shown for centers with <=5 infants or <=1000 hours through November 2005

PERCENT OF TIME SPENT IN SELECTED OXIMETER DISPLAY RANGES MARCH 2006-AUGUST 2006
HOURS ON SUPPLEMENTAL 02 ONLY (THROUGH 36 WEEKS)
(DATA PROCESSED AS OF 8/29/06)

Center	Number of hours	Percent in narrow target 88-92	Percent <84	Percent 84-96	Percent >96
3	9388.1	37.3	11.9	73.2	14.9
9	4618.5	36.8	10.1	72.8	17.2
12	7964.0	25.4	10.7	72.6	16.7
14	8630.7	33.0	11.2	73.5	15.2
16	6375.7	42.1	8.9	75.4	15.7
All centers	**40940.8**	**33.2**	**10.6**	**72.7**	**16.7**

Center data not shown for centers with <=5 infants or <=1000 hours between March 2006 and August 2006

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, September 06, 2006 4:00:19 PM

Hi Rose
Since I can get in and out of Albuquerque in a day, Wade and I can do this at short notice.
If Kristi's preference is to start and then have us or others come, I can live with that. We really want to provide each site with optimal information so that they can enroll well from Day1. I would not force a visit on them.
The times for the meetings are great.
I will stay tuned.
You can call me anytime tomorrow. I will be in the unit/office and so call here at 619 543 3759. I will also leave my cell on – 619 405 (b) (6)
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 06, 2006 9:07 AM
To: Neil Finer
Subject: SUPPORT

Neil –
We will put you on the schedule for the steering committee meeting for 11 AM EST (8 AM PST) on October 11 and 11 AM EST (8AM PST) on October 12.

SUPPORT was approved at New Mexico and Kristi would like to go ahead and begin enrollment prior to training. We had not done this before, but I guess this could be possible. – I need to know what you think. Also, I can try to arrange someone to do the training if you would prefer not to travel. Is there a good time that I can call you tomorrow? I am out of the office this afternoon.

Thanks 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

Blansfield, Earl (NIH/NICHD) [E]

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Tuesday, September 05, 2006 2:35 PM
To: mgantz@rti.org; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org; poo@rti.org
Subject: Re: Oximeter tables

Great. Reassuring. At what rate is the NRN enrolling?
Wally

-----Original Message-----
From: Gantz, Marie <mgantz@rti.org>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>
CC: Das, Abhik <adas@rti.org>; Poole, W. Kenneth <poo@rti.org>
Sent: Tue Sep 05 13:16:49 2006
Subject: RE: Oximeter tables

Actually, nine centers have enrolled 6 or more infants since March, however, not all are included in the tables because we do not have >1000 hours worth of oximeter data that can be confirmed as hours on supplemental oxygen based on form SUPP05. As we receive more oximeter data and more forms SUPP05 we will have more information to include in the tables.

Marie

Marie Gantz, Ph.D.

Research Statistician

RTI International

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 05, 2006 2:05 PM
To: Gantz, Marie; nfiner@ucsd.edu; higginsr@mail.nih.gov
Cc: Das, Abhik; Poole, W. Kenneth
Subject: Re: Oximeter tables

I think these two tables will be usefull. A table of the recently enrilled babies would have to be added.

I am concerned only 4 centers have enrolled 5 or more babies in the 6 months period.
Wally

-----Original Message-----
From: Gantz, Marie <mgantz@rti.org>
To: Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
CC: Das, Abhik <adas@rti.org>; Poole, W. Kenneth <poo@rti.org>
Sent: Tue Sep 05 12:46:34 2006
Subject: Oximeter tables

Hi Neil,

Attached are the tables showing the percent of time spent in each of the oximeter display ranges you specified (<84%, 84-96%, >96% and the narrow target of 88-92%). There is one table for the beginning of the trial through November 2005, and another table for March 2006-August 2006. These tables include only hours (or days) on supplemental oxygen and only day of life 1-14. If you would like me to include days 15+, let me know. Center data are not shown for centers with <=5 infants or <=1000 hours during the given time period, but the totals include data for all centers, including those not shown separately.

Marie

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Neil

From:	Angelita Hensman
To:	Zaterka-Baxter, Kristin; Neil Finer; Wade Rich; Nancy Newman; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc:	Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; mbball@leland.stanford.edu; mcollins@peds.uab.edu; ellen_hale@oz.ped.emory.edu
Subject:	RE: Support Study forms revisions
Date:	Friday, September 01, 2006 1:57:43 PM

Hi Kris,
Do you have the MOP updates/changes to go with these forms?
Thanks
Angelita

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, August 31, 2006 2:50 PM
To: Neil Finer; Wade Rich; Nancy Newman; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; mbball@leland.stanford.edu; mcollins@peds.uab.edu; ellen_hale@oz.ped.emory.edu; Angelita Hensman
Subject: RE: Support Study forms revisions
Importance: High

Please review the attached version of the Supp05, not the one previously sent. This is the correct and most recently updated form.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Thursday, August 31, 2006 11:29 AM
To: 'Neil Finer'; 'Wade Rich'; 'Nancy Newman'; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; 'mbball@leland.stanford.edu'; 'mcollins@peds.uab.edu'; 'ellen_hale@oz.ped.emory.edu'; 'Angelita Hensman'
Subject: RE: Support Study forms revisions

Hi all,
Please find attached improved drafts of the Supp05, Supp05A, Supp06, Supp08 and new Supp12 (replacement oximeter form). Thank you all for your additional suggestion since the initial drafts were reviewed July 19th. Below are a few explanations about these revisions. Please review the forms attached and send any and all comments/suggestions by September 8th.

Supp05:
We've re-worked this form reformatting and renumbering to hopefully make it less confusing. All data points have remained the same with two exceptions; question 14 and 14a (about replacement oximeters) have been deleted because the new Supp12 will capture all oximeter replacement data, and the addition of code '9' (Mode of Support) to document "No support all day and off the study oximeter".

Supp05A

1. We've revised the instructions on this form to clarify its intended use as follows:
Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

2. Based on discussions of relevant blood gas data in relation to intubation/extubation events, it has been decided that the pH, PCO2 and FiO2 should only be reported if within 6 hours prior to the event (as stated already on the Supp07 form). We've added question b(i) below primarily to allow the Data Center to know whether or not to expect blood gas values:
"Were blood gasses obtained within 6 hours prior to the event? If yes, answer 1, 2 & 3 otherwise leave blank"

3. Question 3 and 3a have been deleted because the new Supp12 will capture all oximeter replacement data

Supp06
Two types of protocol deviations have been added as options to select as listed below. We have also renumbered the 'Other' option to code '99' for ease of data programming:
Code 11. Incorrect randomization card select (incorrect gestational age group)
Code 12. Steroids given within 21 days of life.

Supp08
Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting. The data that is intended to be capture are any AEs within the first 14 days of life only. The statement "or prior to study status" has been removed from the instructions on the form. Question 1 has been deleted and AE #1 (Air leak) has been revised removing the statement "*in the first 14 days*"

New Supp12
This new form will capture all study oximeter replacement data throughout the study period from initiation to 36 weeks or status. We've clarified the instructions on the top of this form as follows:
"Complete this form each time a ~~replacement~~ study oximeter is ~~used~~ replaced from study initiation to 36 weeks or status"

MRI01
This form has been recently revised. To allow the option of recording that the early cranial US was not done, we've added the following question:
"Was the early cranial US preformed?"

In addition, we've added two options under Section B and C for coding reasons for an abnormal CUS:
--"Evolving or resolving IVH?"
--"Other (Specify)"

Revisions to the MOP are forthcoming. Your comments and suggestions are greatly appreciated.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
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Cc:	Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; mbball@leland.stanford.edu; mcollins@peds.uab.edu; ellen_hale@oz.ped.emory.edu; Angelita Hensman
Subject:	RE: Support Study forms revisions
Date:	Thursday, August 31, 2006 2:50:10 PM
Attachments:	SUPP05SafetyMonitorRev08 31 06.doc
Importance:	High

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Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
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Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Thursday, August 31, 2006 11:29 AM
To: 'Neil Finer'; 'Wade Rich'; 'Nancy Newman'; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Cc: Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; 'mbball@leland.stanford.edu'; 'mcollins@peds.uab.edu'; 'ellen_hale@oz.ped.emory.edu'; 'Angelita Hensman'
Subject: RE: Support Study forms revisions

Hi all,
Please find attached improved drafts of the Supp05, Supp05A, Supp06, Supp08 and new Supp12 (replacement oximeter form). Thank you all for your additional suggestion since the initial drafts were reviewed July 19th. Below are a few explanations about these revisions. Please review the forms attached and send any and all comments/suggestions by September 8th.

Supp05:
We've re-worked this form reformatting and renumbering to hopefully make it less confusing. All data points have remained the same with two exceptions; question 14 and 14a (about replacement oximeters) have been deleted because the new Supp12 will capture all oximeter replacement data, and the addition of code '9' (Mode of Support) to document "No support all day and off the study oximeter".

Supp05A
1. We've revised the instructions on this form to clarify its intended use as follows:
Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

2. Based on discussions of relevant blood gas data in relation to intubation/extubation events, it has been decided that the pH, PCO2 and FiO2 should only be reported if within 6 hours prior to the event (as stated already on the Supp07 form). We've added question b(i) below primarily to allow the Data Center to know whether or not to expect blood gas values:
"*Were blood gasses obtained within 6 hours prior to the event? If yes, answer 1, 2 & 3 otherwise leave blank*"

3. Question 3 and 3a have been deleted because the new Supp12 will capture all oximeter replacement data

Supp06

Two types of protocol deviations have been added as options to select as listed below. We have also renumbered the 'Other' option to code '99' for ease of data programming:

Code 11. Incorrect randomization card select (incorrect gestational age group)

Code 12. Steroids given within 21 days of life.

Supp08

Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting. The data that is intended to be capture are any AEs within the first 14 days of life only. The statement "or prior to study status" has been removed from the instructions on the form. Question 1 has been deleted and AE #1 (Air leak) has been revised removing the statement "*in the first 14 days*"

New Supp12

This new form will capture all study oximeter replacement data throughout the study period from initiation to 36 weeks or status. We've clarified the instructions on the top of this form as follows:

"Complete this form each time a ~~replacement~~ study oximeter is ~~used~~ replaced from study initiation to 36 weeks or status"

MRI01

This form has been recently revised. To allow the option of recording that the early cranial US was not done, we've added the following question:

"Was the early cranial US preformed?"

In addition, we've added two options under Section B and C for coding reasons for an abnormal CUS:

--"Evolving or resolving IVH?"

--"Other (Specify)"

Revisions to the MOP are forthcoming. Your comments and suggestions are greatly appreciated.

Thanks,
Kris

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
SAFETY MONITORING FORM

SUPP05 Rel 4.0
October 3, 2005
Revised March 7, 200
Revised August 31, 2006

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete a form each day through DOL 14 **1. Study Day:** __ __ **2. Date:** __ __ / __ __ / __ __ __ __.

3. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
2. 04 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
3. 06 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
4. 08 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
5. 10 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
6. 12 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
7. 14 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
8. 16 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
9. 18 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
10. 20 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
11. 22 : 00	__ __ : __ __	__. __ __	____	__. __ __ __	____
12. 23 : 59	__ __ : __ __	__. __ __	____	__. __ __ __	____

5. Oximeter Alarm Checks Q6hr/day

a. __ __ : __ __

b. __ __ : __ __

c. __ __ : __ __

d. __ __ : __ __

6. Was the Infant intubated or extubated on this day? **Y** **N**

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

4. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 08 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	____	____	__. __ __ __	____
2. 16 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	____	____	__. __ __ __	____
3. 23 : 59	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	____	____	__. __ __ __	____

*Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

5-03532

From: Susan Hintz
To: Angelita Hensman
Cc: adas@rti.org; alaptook@WIHRI.org; Higgins, Rosemary (NIH/NICHD) [E]; joa@rti.org
Subject: Re: SUPPORT/MRI study question
Date: Thursday, August 31, 2006 2:19:25 PM

Hi Angelita,

Thanks so much for follow-up with this. I would LOVE to have this baby in the SUPPORT Neuroimaging study! I am assuming from your email that an "early" cranial US was already obtained, and if the baby will be 36 weeks (b) (6), you could get both the "late" cranial US and MRI. If there are missing oximeter data, it would not affect the Neuroimaging secondary analysis.

Thanks again for bird-dogging this issue!

Susan

> Hi all,
>
> We had a SUPPORT study infant who was transferred to a level 2 hospital and then readmitted back to our NICU after almost 3 weeks so we take the "transfer" date as status for GDB and SUPPORT. The baby was transferred at around 31 weeks and was taken off the SUPPORT study p.o at that time. The baby is going to be 36 weeks old (b) (6) (b) (6) Should we get consent for the MRI study and enroll the baby? Would we be missing too much pulse oximeter data? Also, would there be a problem entering the form because the baby is considered transferred?
>
> Susan: Would you want this infant enrolled in the MRI study if we can get consent?
>
> Thanks
>
> Angelita

--

Susan R. Hintz, M.D., M.S. Epi
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: Auman, Jeanette O.
To: Angelita Hensman; Das, Abhik; Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook
Subject: RE: SUPPORT/MRI study question
Date: Thursday, August 31, 2006 11:55:03 AM

You won't have trouble entering the form into the data entry system if Susan feels the infant should be enrolled.

Jenny

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, August 31, 2006 11:11 AM
To: Auman, Jeanette O.; Das, Abhik; Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook
Subject: SUPPORT/MRI study question

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Susan: Would you want this infant enrolled in the MRI study if we can get consent?

Thanks
Angelita

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Cc:	Auman, Jeanette O.; Pickett, James; Petrie, Carolyn; mbball@leland.stanford.edu; mcollins@peds.uab.edu; ellen_hale@oz.ped.emory.edu; Angelita Hensman
Subject:	RE: Support Study forms revisions
Date:	Thursday, August 31, 2006 11:28:59 AM
Attachments:	SUPP05SafetyMonitor[Rev08.31.06].doc SUPP05ASafetyMonitor[08.31.06](uc).doc SUPP06 Prot Dev[08.31.06](uc).doc SUPP08Adverse Event[08.31.06]Rev.doc SUPP12 oximeter replacement 08.31.06.doc MRI Enrollment Form MRI01 08 31 06 SH (uc).doc

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Complete a form each day through DOL 14 **1. Study Day:** __ __ **2. Date:** __ __ / __ __ / __ __ __ __.

A. FiO2: Record FiO2 and respiratory support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) FiO_2	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
2. 04 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
3. 06 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
4. 08 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
5. 10 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
6. 12 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
7. 14 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
8. 16 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
9. 18 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
10. 20 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
11. 22 : 00	__ __ : __ __	__. __ __	___	__. __ __ __	___
12. 23 : 59	__ __ : __ __	__. __ __	___	__. __ __ __	___

17. Oximeter Alarm Checks Q6hr/day

1. __ __ : __ __
2. __ __ : __ __
3. __ __ : __ __
4. __ __ : __ __

18. Was the Infant intubated or extubated on this day? **Y** **N**

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

B. Blood Gas Information: Record blood gas results closest to the Scheduled Time, if available.

(a) Scheduled Time	(b) Time Measured (hour : min)	(c) pH	(d) CO2	(e) PO2	(f) FiO_2	(g)* Source	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
14. 08 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
15. 16 : 00	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___
16. 23 : 59	__ __ : __ __	__. __ __	__ __ __	__ __ __	__. __ __	___	___	__. __ __ __	___

* Source	1= Arterial	2= Venous	3= Capillary

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9=No Support all day and off Study oximeter

***CPAP Type	2= Ventilator	4= Bubble	6 = Flow Driver	9= Other

ource	1= Arterial	2= Venous	3 = Capillary

5-03537

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

SUPP05A version 3.0
Revised June 5, 2006
Revised August 31, 2006

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Report ~~This form should be completed~~ each time an intubation/extubation occurs ~~in the same day.~~ Number each event sequentially.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __** C.

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 :
i. Were blood gasses obtained within 6 hours prior to the event? If yes, answer 1, 2 & 3 otherwise leave blank." Y N

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 __ __ __

DELETERD QUESTION #3 AND 3a – see new form SUPP12

Initials of person completing this form: __ __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 :
i. Were blood gasses obtained within 6 hours prior to the event? If yes, answer 1, 2 & 3 otherwise leave blank." Y N

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 __ __ __

DELETED QUESTION #3 AND 3a – see new form SUPP12

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)***~~
   11. **Incorrect randomization card select (incorrect gestational age group)**
   12. **Steroids given within 21 days of life.**
   99. **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: ___

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: __ __ __

The Surfactant, Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Replacement Oximeter Form

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

Complete this form each time a ~~replacement~~ study oximeter is ~~used~~ replaced from study initiation to 36 weeks or status.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
2.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
3.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
4.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
5.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
6.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
7.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
8.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
9.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___
10.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __ __	___

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

Was the early cranial US preformed? Y N

1. Date of early cranial US __ __/__ __/__ __ __ __ (Month Day Year)

(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)* :

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
j. Evolving or resolving IVH?	Y	N	Y	N
k. Other (Specify) _____	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/reservoir in place?	Y	N	Y	N
f. Evolving or resolving IVH?	Y	N	Y	N
g. Other (Specify) _____	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

From: Wally Carlo, M.D.
To: nfiner@ucsd.edu; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: wrich@ucsd.edu; mgantz@rti.org; poo@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Oximeter data for the SUPPORT Trial
Date: Monday, August 28, 2006 7:33:32 AM

Neil:

Great! Let see what the others think.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; ALaptook@wihri.org <ALaptook@wihri.org>; adas@rti.org <adas@rti.org>; mcw3@case.edu <mcw3@case.edu>; Bradley.Yoder@hsc.utah.edu <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; nxs5@case.edu <nxs5@case.edu>
CC: Wade Rich <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>
Sent: Sun Aug 27 22:10:11 2006
Subject: RE: Oximeter data for the SUPPORT Trial

Hi Wally
This sounds fine to me. We would produce the first 3 months with 3 monthly updates.
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, August 27, 2006 4:27 PM
To: Neil Finer; Wally Carlo, M.D.; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; higginsr@mail.nih.gov
Subject: Re: Oximeter data for the SUPPORT Trial

Neil: I think that would be an obvious break(before and after the interruption of the trial. Alson we could keep breaking the data and give the most recent (e.g. Every 3 months) separate so each center as well as us can monitor better ongoing performance.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; ALaptook@wihri.org <ALaptook@wihri.org>; adas@rti.org <adas@rti.org>; mcw3@case.edu <mcw3@case.edu>; Bradley.Yoder@hsc.utah.edu <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; nxs5@case.edu <nxs5@case.edu>
CC: Wade Rich <wrich@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>
Sent: Sun Aug 27 19:22:02 2006

Subject: RE: Oximeter data for the SUPPORT Trial

Wally

Are you suggesting that we break out the data from before Nov 20 2005 and after Mar 2006, and send both??

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, August 27, 2006 3:46 PM
To: Neil Finer; ALaptook@wihri.org; adas@rti.org; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; mgantz@rti.org; poo@rti.org; higginsr@mail.nih.gov
Subject: Re: Oximeter data for the SUPPORT Trial

I think it is important to have recent data separate from past data so each center can determine if they have a improving or worsening performance.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Abbot Laptook <ALaptook@wihri.org>; Das, Abhik <adas@rti.org>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; mcw3@case.edu <mcw3@case.edu>; Bradley.Yoder@hsc.utah.edu <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; nxs5@case.edu <nxs5@case.edu>
CC: Wade Rich <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Poole, W. Kenneth <poo@rti.org>; higginsr@mail.nih.gov <higginsr@mail.nih.gov>
Sent: Sun Aug 27 16:47:00 2006
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone

Thanks for your replies

I agree and would suggest that we send each center that has enrolled > 5 infants their data, as the overall data.

I would suggest that we use a Table which shows the following ranges

< 84%, 84%-96%, 88%-92% > 96%. This will show the narrow target and the low and high ranges that we have agreed to use.

I had asked Marie to prepare all of the data for which we use time in Oxygen as either all 3 times in a day (before DSMC) or more recently using the 2 hour blocks. While the 2 hour blocks are not perfect, they are a big improvement.

In addition Marie has initially sent the data only from March onward representing about 7200 hours and the time b/n 88-92% was 41% for 3 centers with a range from 36% to 48%. When she combined these with overall data for oxygen the percent was 38%, with a range of 29.6 to 42.5% for about 32,500 hours, not really different. Since the study will use all the data, I would prefer to use all the data in oxygen to this point.

For sites with less than 5 enrollees, we can either send them the overall data, my preference, so that they can see the amount of babies and hours as an encouragement, or send them nothing till they have enrolled.

Let me know if you agree and I would then ask Marie and Rose to send the relevant data to the sites. I will continue to follow the Oximeter downloads, and if there enough additional data, perhaps we can send out the next version in less than 3 months.

Thanks for you input. I will look forward to your responses.

Be well

Neil

From: Abbot Laptook [mailto:ALaptook@wihri.org]
Sent: Friday, August 25, 2006 4:20 PM
To: Das, Abhik; Wally Carlo, M.D.; Neil Finer; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: Wade Rich; Gantz, Marie; Poole, W. Kenneth; higginsr@mail.nih.gov
Subject: RE: Oximeter data for the SUPPORT Trial

I am good with the suggestions; sites definitely need to see their data and it is nice to compare to the total. AL

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, August 25, 2006 11:36 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; Abbot Laptook; kurt.schibler@cchmc.org; nxs5@case.edu
Cc: wrich@ucsd.edu; Gantz, Marie; Poole, W. Kenneth; higginsr@mail.nih.gov
Subject: RE: Oximeter data for the SUPPORT Trial

On average sites are accruing 1-3 infants per month. Given this rate, we think it makes sense to send these reports out on a quarterly basis. We can perhaps separate out the last 4-6 months of data accrued to show more recent results and yet have enough numbers per site for it to be meaningful.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, August 25, 2006 10:56 AM

To: Das, Abhik; higginsr@mail.nih.gov; nfiner@ucsd.edu; mcw3@case.edu; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; ALaptook@wihri.org; kurt.schibler@cchmc.org; nxs5@case.edu; Gantz, Marie; Poole, W. Kenneth
Cc: wrich@ucsd.edu
Subject: Re: Oximeter data for the SUPPORT Trial

I also agree. I think this type of feedback is helpful. We should think of how frequebtly it should be sent and whether it would also be helpful to have recent data also shown separately so each site can determine if their performance is improving or worsening compared to themselves.
Wally

-----Original Message-----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Michele Walsh <mcw3@case.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger Faix <Roger.Faix@hsc.utah.edu>; Abbot Laptook <ALaptook@wihri.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Nancy Newman <nxs5@case.edu>; Gantz, Marie <mgantz@rti.org>; Poole, W. Kenneth <poo@rti.org>
CC: Wade Rich <wrich@ucsd.edu>
Sent: Fri Aug 25 09:24:46 2006
Subject: RE: Oximeter data for the SUPPORT Trial

I agree. Sites should get their individual data, plus the overall average.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 10:21 AM
To: Neil Finer; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

This looks very good. I think it should go out by site only, unless the data are de-identified. If the data site ID's are removed, it can be shared.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thu 8/24/2006 11:44 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
I am attaching information about the oximeter data using all available baby data for time in oxygen since the trial began. It includes the infant enrolled prior to the stoppage for which we used in oxygen at all 3 time points in a day and the infants subsequently enrolled for whom we use the 2 hourly data to determine if they are in oxygen.
Do you think that we should send this information to all centers, only those that have enrolled, or none at this time?
Thanks for your input.
Regards
Neil

From: Wally Carlo, M.D.
To: Walsh, Michele; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Friday, August 25, 2006 1:25:26 PM

I agree. Overall, each center could improve. wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@uhhs.com]
Sent: Friday, August 25, 2006 12:21 PM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hi Neil:
Thanks for the data! When we get the final version I will share with staff.
Is it a problem that the percentage >92% is so high? If not I would not distribute the second graph. If I recall correctly, we said on the subcommittee and at steering committee that we would only look at the top distribution. Michele

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, August 24, 2006 11:45 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Wade Rich
Subject: RE: Oximeter data for the SUPPORT Trial

Hello Everyone
I am attaching information about the oximeter data using all available baby data for time in oxygen since the trial began. It includes the infant enrolled prior to the stoppage for which we used in oxygen at all 3 time points in a day and the infants subsequently enrolled for whom we use the 2 hourly data to determine if they are in oxygen.
Do you think that we should send this information to all centers, only those that have enrolled, or none at this time?

Thanks for your input.
Regards
Neil

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Oximeter data for the SUPPORT Trial
Date: Friday, August 25, 2006 11:39:06 AM

Yes; you have!
Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 11:35 AM
To: Das, Abhik
Subject: Re: Oximeter data for the SUPPORT Trial

I have them all and am putting the info together - Bottom line appears to be - the better the comminication with OB and the neonatal team, the better the recruitment. Weekend and night availability (whether research or clinical staff) to obtain consents also seems to help.
Did I answer all of your emails - I have been out of the office all week

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Aug 25 11:32:13 2006
Subject: RE: Oximeter data for the SUPPORT Trial

I agree! Did you get many responses to your earlier questionnaire to the sites on this issue?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 11:31 AM
To: Das, Abhik; Gantz, Marie; Poole, W. Kenneth
Subject: Re: Oximeter data for the SUPPORT Trial

I am hoping the opposite - accrural needs to speed up!!!!
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie <mgantz@rti.org>; Poole, W. Kenneth <poo@rti.org>
Sent: Fri Aug 25 11:28:41 2006

Subject: RE: Oximeter data for the SUPPORT Trial

I think that sending out quarterly reports should be fine. Down the line, if accrual slows down (hopefully not!), then we can revisit the issue.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 11:26 AM
To: Gantz, Marie; Poole, W. Kenneth; Das, Abhik
Subject: Re: Oximeter data for the SUPPORT Trial

I had envisioned no more often every 3 months - definately less often if there is unblinding concern (like 4-6 months).
You folks should decide this as the investigators will likely want the info more often, not to "unblind" but to do a better job.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Gantz, Marie <mgantz@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Poole, W. Kenneth <poo@rti.org>; Das, Abhik <adas@rti.org>
Sent: Fri Aug 25 11:20:17 2006
Subject: RE: Oximeter data for the SUPPORT Trial

Since the program is already written, it does not take much time to generate the data. The main concern that Abhik, Ken and I have discussed with Neil is the potential for unblinding if we send the data too often. Below is an excerpt from an email I sent Neil:

"Also, Abhik, Ken and I have had discussions about the possibility that centers could become unblinded by viewing these tables. The problem is that, in the high O2 group, the oximeter display values >92% correspond to actual values >95%, and for the low O2 group they correspond to actual values >89%. Meanwhile, in both groups, display values >96% correspond to actual values >96%. As a result, the difference in the percent of time spent at display values of >92% and >96% has the potential to be much larger in the low O2 group than it is in the high O2 group. A similar issue exists for the display values <88% and <84%. Thus, if centers have more infants in one treatment group, especially if they have very few infants total, they could potentially figure out whether they had more high O2 or low O2 babies by comparing the tables for the wide and narrow targets. Furthermore, if they were aware that they have had more "orange" babies since March, they could figure out which treatment group corresponds to that color. For this reason, we have limited the center totals displayed in the attached tables to those centers with at least 3 infants in each oximeter group and with at least 1000 hours of data. The table totals include data from all centers, including those for whom individual data are not displayed."

Neil agreed that we should be cautious in sending out the data too frequently. We discussed the possibility of sending the reports quarterly, since the centers tend to enroll 1-3 infants per month. If we are going to send reports that show recent data broken out separately, I would not recommend sending them more often than quarterly. If the sites already have a substantial amount of data, and recent data are not broken out separately, we might be able to send reports more frequently without the risk of unblinding.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 11:02 AM
To: Gantz, Marie; Poole, W. Kenneth; Das, Abhik
Subject: Fw: Oximeter data for the SUPPORT Trial

I would agree that this is extremely helpful. How often do you recommend that this info be generated for the sites?? Also, how much time does it take to generate these data?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: adas@rti.org <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; mcw3@case.edu <mcw3@case.edu>; Bradley.Yoder@hsc.utah.edu <Bradley.Yoder@hsc.utah.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; ALaptook@wihri.org <ALaptook@wihri.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; nxs5@case.edu <nxs5@case.edu>; mgantz@rti.org <mgantz@rti.org>; poo@rti.org <poo@rti.org>
Cc: wrich@ucsd.edu <wrich@ucsd.edu>
Sent: Fri Aug 25 10:56:29 2006
Subject: Re: Oximeter data for the SUPPORT Trial

I also agree. I think this type of feedback is helpful. We should think of how frequebtly it should be sent and whether it would also be helpful to have recent data also shown separately so each site can determine if their performance is improving or worsening compared to themselves.
Wally

-----Original Message-----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Michele Walsh <mcw3@case.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger Faix <Roger.Faix@hsc.utah.edu>; Abbot Laptook <ALaptook@wihri.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Nancy Newman <nxs5@case.edu>; Gantz, Marie <mgantz@rti.org>; Poole, W. Kenneth <poo@rti.org>
CC: Wade Rich <wrich@ucsd.edu>
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Subject: RE: Oximeter data for the SUPPORT Trial

I agree. Sites should get their individual data, plus the overall average.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 25, 2006 10:21 AM
To: Neil Finer; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
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Sent: Thu 8/24/2006 11:44 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
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Do you think that we should send this information to all centers, only

those that have enrolled, or none at this time?
Thanks for your input.
Regards
Neil

From:	Neil Finer
To:	Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc:	Wade Rich
Subject:	RE: Oximeter data for the SUPPORT Trial
Date:	Thursday, August 24, 2006 11:44:29 AM
Attachments:	Pct in range for all enrolled (supp O2) 8-22-06.rtf

Hello Everyone
I am attaching information about the oximeter data using all available baby data for time in oxygen since the trial began. It includes the infant enrolled prior to the stoppage for which we used in oxygen at all 3 time points in a day and the infants subsequently enrolled for whom we use the 2 hourly data to determine if they are in oxygen.
Do you think that we should send this information to all centers, only those that have enrolled, or none at this time?
Thanks for your input.
Regards
Neil

PERCENT OF TIME SPENT IN EACH OXIMETER DISPLAY RANGE SINCE ENROLLMENT BEGAN

FIRST 14 DAYS OF LIFE (DAYS ON SUPPLEMENTAL 02 ONLY)

(DATA RECEIVED AS OF 8/16/2006)

Center	Hours	Percent in display range <84	Percent in display range 84-96	Percent in display range >96
3	3814.5	10.6	80.9	8.5
8	1447.8	6.6	73.3	20.1
9	2940.8	11.0	75.7	13.2
11	1946.7	9.3	75.6	15.1
12	2870.9	7.0	82.0	11.0
14	5234.0	8.5	83.1	8.3
16	5498.1	9.5	81.4	9.2
18	2066.1	10.4	77.6	12.0
20	1860.4	7.5	74.1	18.4
22	3322.5	8.6	79.5	11.9
Total	**32508.1**	**9.0**	**79.6**	**11.4**

Center	Hours	Percent in display range <88	Percent in display range 88-92	Percent in display range >92
3	3814.5	20.4	38.6	41.0
8	1447.8	14.7	29.6	55.7
9	2940.8	24.8	38.7	36.6
11	1946.7	20.9	36.9	42.3
12	2870.9	19.1	40.8	40.1
14	5234.0	20.6	39.9	39.5
16	5498.1	21.5	42.5	36.0
18	2066.1	19.7	31.1	49.2
20	1860.4	16.0	30.8	53.2
22	3322.5	19.5	40.1	40.3
Total	**32508.1**	**20.1**	**38.3**	**41.6**

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP questions for SUPPORT
Date: Wednesday, August 16, 2006 2:40:41 PM

Rose:

At this point it does not look like we will have the required number of babies reach status before December; so a meeting would likely be in January or February 2007. We could make that one face-to-face.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, August 16, 2006 2:07 PM
To: Das, Abhik
Subject: RE: ROP questions for SUPPORT

Abhik –
DO you have a date yet fro the meeting? Also, we should have a face-to-face DSMC meeting within the next 9-12 months.

Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, August 16, 2006 1:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ROP questions for SUPPORT

FYI

From: Gantz, Marie
Sent: Wednesday, August 16, 2006 1:10 PM
To: Phelps, Dale
Cc: 'Neil Finer'; Das, Abhik; Poole, W. Kenneth
Subject: ROP questions for SUPPORT

Hi Dale,

I am preparing for the first interim analysis of the SUPPORT data, and I have a few questions about determining the primary outcome of "severe ROP (threshold disease or the need for surgery)." If you could answer them for me, I would greatly appreciate it.

1) Does the infant have threshold disease if, on SUPP10, **Threshold (New Type I)** = Y in either eye, at any exam?
2) I can obviously look at the SUPP10 variable for **Surgery** to see if the infant had surgery on the day of the recorded exam, but should I also be looking at other variables (such as **Post-surgical Retinal Detachment**) in case an exam was not performed on the actual day of surgery? How can I be sure to pick up on all of the surgeries?
3) The criteria for determining acute/final status includes the unfavorable outcomes of Retinal

detachment stage 4b or 5. Do I find that in the **Highest Stage in any Zone** field?

4) What SUPP10 fields would I use to determine the favorable outcomes:
   a. Vessel growth if mature to the ora serrata in all clock hours
   b. Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)
5) Is it possible for an infant to have retinal detachment stage 4b or 5, but not threshold disease or surgery? If so, how would such an infant be classified in terms of the ROP primary outcome?

Thanks in advance for your help! If you think it would be easier to talk over the phone, that would be fine with me.

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

From: Zaterka-Baxter, Kristin
To: Mcdavid, Georgia E; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Brunson, Anne L
Cc: Morris, Brenda H
Subject: RE: SUPPORT study death
Date: Wednesday, August 16, 2006 11:54:19 AM

Thanks Georgia, Please also complete the Medwatch form (Supp08A) if you have not already done so and fax it to both Rose (301-496-3790) and myself (919-485-7762).
Very Much appreciated,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Mcdavid, Georgia E [mailto:Georgia.E.McDavid@uth.tmc.edu]
Sent: Wednesday, August 16, 2006 11:45 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Brunson, Anne L
Cc: Zaterka-Baxter, Kristin; Morris, Brenda H
Subject: SUPPORT study death

Infant (b) (6) (SUPPORT study) expired (b) (6) The COD is likely sepsis however is unproven by culture. The infant was well passed the 14 day study intervention period and it is unlikely participation in the study caused his death.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Important: unmasking and choice of cut-offs for histogram"bins"on Masimo study oximeters
Date: Tuesday, August 15, 2006 4:53:00 PM

Absolutely
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 15, 2006 11:28 AM
To: Neil Finer
Cc: Wade Rich
Subject: RE: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Neil
I had Abhik take a look at this - can we remove the colors from the spreadsheet and then send it out for a vote??
Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 15, 2006 12:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Hi Rose
Here is the data that we calculated for the Masimo and the other trials. I am concerned that our PIs will become worried or confused about this - this is not a problem for SUPPORT. All of our oximeters including the newer ones sent to Alabama were reconfigured for the Old Histogram.
Thus the New histogram is NOT an issue for SUPPORT.
I hope that we can get approval to share these calculations. They represent 24 hours of data for 6 infants and we are not unblended to the actual oximeter skew. In addition we are not sharing any raw data with anyone. The data shown here are calculated ranges.
Every other Trial PI has now requested this information, and I believe that this will reduce their concerns about the new histogram - but perhaps not.
At least we are trying to help.
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 15, 2006 6:13 AM
To: Neil Finer
Cc: Wade Rich

Subject: RE: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Neil
Can you send me the items that you wish to share?
Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, August 14, 2006 6:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Hi Rose
Yes that would be good. These are only 24 hours of data from 3 infants, and we calculated the differences. In addition, we also will have 2 different skews if any sites were sent new oximeters.
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 14, 2006 2:23 PM
To: Neil Finer
Subject: Fw: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Neil
This needs to go through the steering committee and the director. The reason is valid. Would you like me to poll folks?

Thanks for your commitment!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: William Tarnow-Mordi <williamtm@med.usyd.edu.au>
To: Brian Darlow <brian.darlow@chmeds.ac.nz>
Cc: Neil Finer <nfiner@ucsd.edu>; msayre@masimo.com <msayre@masimo.com>; Professor Colin Morley <colin.morley@wch.org.au>; Lex Doyle <lwd@unimelb.edu.au>; Peter Davis <pgd@unimelb.edu.au>; Stenson, Ben <Ben.Stenson@luht.scot.nhs.uk>; Barbara Schmidt <schmidt@mcmaster.ca>; Edmund Hey <shey@easynet.co.uk>; Robin Roberts <robertsr@mcmaster.ca>; Robin K Whyte <robin.whyte@dal.ca>; Christian F Poets <christian-f.poets@med.uni-tuebingen.de>; Jack Rabi <Jack.Rabi@calgaryhealthregion.ca>; Wade Rich <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Aug 14 18:16:40 2006
Subject: RE: Important: unmasking and choice of cut-offs for histogram'bins'on Masimo study oximeters

Dear Neil

Thank you for offering to share this data. I would appreciate receiving it to share with the Australian BOOST II investigators.

William

Quoting Brian Darlow <brian.darlow@chmeds.ac.nz>:

> Dear Neil, Many thanks for doing this. We have Radicals with the "new"
> histogram for the BOOST-NZ trial. So I would very much appreciate being
> able to see your data. Kind regards, Brian
>
> At 10:51 AM 8/14/2006 -0700, Neil Finer wrote:
>
>> Hello Maribeth,
>> As we discussed on the phone last week, we have done some
>> testing of the two histograms, the one currently used in SUPPORT and the
>> new one available in the Rev. 5 Radicals. We used real data from our
>> own babies in the trial for 24 hour segments of time, since this is the
>> longest option for the histogram. We used both high and low oximeters,
>> though we do not know which is which.
>> We would be happy to share this data with any of the
>> investigators who are concerned about the histogram at their request.
>>
>> Neil Finer, MD
>> PI, SUPPORT Trial
>>
>> Wade Rich, BSHS, RRT
>> Coordinator, SUPPORT Trial

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: Important: unmasking and choice of cut-offs for histogram"bins"on Masimo study oximeters
Date: Tuesday, August 15, 2006 12:25:06 PM
Attachments: Histograms new vs old Aug 14 06 revised.xls

Hi Rose
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Sent: Tuesday, August 15, 2006 6:13 AM
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Sent from my BlackBerry Wireless Handheld

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To: Brian Darlow <brian.darlow@chmeds.ac.nz>
Cc: Neil Finer <nfiner@ucsd.edu>; msayre@masimo.com <msayre@masimo.com>; Professor Colin Morley <colin.morley@wch.org.au>; Lex Doyle <lwd@unimelb.edu.au>; Peter Davis <pgd@unimelb.edu.au>; Stenson, Ben <Ben.Stenson@luht.scot.nhs.uk>; Barbara Schmidt <schmidt@mcmaster.ca>; Edmund Hey <shey@easynet.co.uk>; Robin Roberts <robertsr@mcmaster.ca>; Robin K Whyte <robin.whyte@dal.ca>; Christian F Poets <christian-f.poets@med.uni-tuebingen.de>; Jack Rabi <Jack.Rabi@calgaryhealthregion.ca>; Wade Rich <wrich@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
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>>
>> Neil Finer, MD
>> PI, SUPPORT Trial
>>
>> Wade Rich, BSHS, RRT
>> Coordinator, SUPPORT Trial

ORANGE

Bin new	*Frequency*	Percent	*Bin old*	*Frequency*	Percent	*Bin new*	*Frequency*	Percent	*Bin old*	*Frequency*	Percent	*Bin new*	*Frequency*	Percent	*Bin old*	*Frequency*	Percent
≤ 84	4930.0	11.3	< 83	4731.0	10.8	≤ 84	2333.0	5.3	< 83	1575.0	3.6	≤ 84	9741.0	22.1	< 83	3811.0	8.7
85-87	246.0	0.6	84-87	445.0	1.0	85-87	866.0	2.0	84-87	1624.0	3.7	85-87	5421.0	12.3	84-87	11351.0	25.8
88-92	1503.0	3.4	88-92	1503.0	3.4	88-92	15216.0	34.6	88-92	15216.0	34.6	88-92	21330.0	48.5	88-92	21330.0	48.5
93-95	2261.0	5.2	93-96	11233.0	25.6	93-95	6821.0	15.5	93-96	12802.0	29.1	93-95	2466.0	5.6	93-96	4008.0	9.1
>95	34872.0	79.6	> 96	25900.0	59.1	>95	18763.0	42.6	> 96	12782.0	29.1	>95	5041.0	11.5	> 96	3499.0	8.0
Sum	43812.0	100.0		43812.0			43999.0			43999.0			43999.0	100.0		43999.0	

BLUE

Bin new	*Frequency*		*Bin old*	*Frequency*	Percent	*Bin new*	*Frequency*	Percent	*Bin old*	*Frequency*	Percent	*Bin new*	*Frequency*	Percent	*Bin old*	*Frequency*	Percent
≤ 84	7505.0	17.1	< 83	5174.0	11.8	≤ 84	3801.0	11.2	< 83	2051.0	6.0	≤ 84	5063.0	11.5	< 83	2214.0	5.0
85-87	2395.0	5.4	84-87	4726.0	10.7	85-87	1771.0	5.2	84-87	3521.0	10.4	85-87	2745.0	6.2	84-87	5594.0	12.7
88-92	11924.0	27.1	88-92	11924.0	27.1	88-92	11917.0	35.1	88-92	11917.0	35.1	88-92	19103.0	43.4	88-92	19103.0	43.4
93-95	3166.0	7.2	93-96	6081.0	13.8	93-95	3456.0	10.2	93-96	6266.0	18.5	93-95	5081.0	11.5	93-96	8559.0	19.5
>95	19009.0	43.2	> 96	16094.0	36.6	>95	12993.0	38.3	> 96	10183.0	30.0	>95	12007.0	27.3	> 96	8529.0	19.4
	43999.0	100.0	0.0	43999.0	100.0		33938.0	100.0		33938.0	100.0		43999.0	100.0		43999.0	

For old Histogram Orange
1% 3% and 25% between 84-87
25% 29% and 9% between 93-96%

For New histogram Orange
.5% 1.9% 12.3% between 85-87
5%, 15% and 5% between 93-95%

For Old Histogram Blue
13%, 18% 19% between 93-96
10% 10% and 12% between 84-87

For New Histogram Blue
7% 10% and 11% between 93-95%
5%, 5% and 6% between 85-87

From: Monica Collins
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT enrolment
Date: Monday, August 14, 2006 4:02:12 PM

For us, in our units, it is very important for us to come in for a period of time. High visibility reminds all of the nurses and therapists that we have a job to do and should do it the best of our ability. Often times, we are the first one to identify and only ones who have time to talk with the families on the weekends.

If it works well for other units to call in, that's great but I think in our particular situation, it is important for visibility as they may not know us by name, but absolutely by face. We also prevent protocol violations because we are available to the staff and check in on every support baby (existing- very 24 hours) and (new--usually within 12 hours).
Monica

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 8/14/2006 2:07 PM
To: Wally Carlo, M.D.
Cc: Monica Collins
Subject: RE: SUPPORT enrolment

Wally and Monica –
Some sites (both successful and unsuccessful at recruitment) have the research nurses "call in" to the labor floor, labor and delivery and NICU to assist with recruitment on the weekends. Do you believe that "presence of the nurse" routinely coming in on the weekends positively affects recruitment or do you think that "calling in" is adequate (depending on the relationship of the research nurses with the staff, of course)??
Thanks
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, August 14, 2006 2:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins
Subject: RE:SUPPORT enrolment

Rose:

1) Enroll 24 hours a day,
2) Get notified by Ob upon admission of a Mom 24-27 weeks,
3) Check the Ob "board" routinely twice a day,
4) A research nurse routinely comes in during the weekends.

I am copying Monica in case she has other ideas.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 14, 2006 1:16 PM
To: Wally Carlo, M.D.; jon.e.tyson@uth.tmc.edu; Monica Collins; Georgia.E.McDavid@uth.tmc.edu
Subject: FW:

HI,
I am missing a couple of SUPPORT recruitment strategy documents. Since your sites are "high recruiters," it is very likely that information you could provide would be helpful for the trial. Please fill this out as best as you can and return it to me.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, August 01, 2006 9:28 AM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; Ambal (ambal@uab.edu); Av Fanaroff (aaf2@po.cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Ivan Frantz'; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); 'Kristi Watterberg'; Kurt Schibler (Kurt Schibler [kurt.schibler@cchmc.org]); Michael Cotten (cotte010@mc.duke.edu); 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; papile@unm.edu; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (walid.salhab@utsouthwestern.edu); Angelita Hensman; Anne Furey (afurey@tufts-nemc.org); Becky bara; Bethany Ball; Cathy Grisby; Conra Backstrom; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); Kathy Auten; Lucy Miller; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; susan.tepper@hsc.utah.edu
Cc: 'Petrie, Carolyn'; Zaterka-Baxter, Kristin; Neil Finer
Subject:

Hi:

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment. We are particularly interested in "successful strategies for recruitment" that have enhanced trial enrollment.
please return the survey by Monday August 7.

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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins
Subject: RE: SUPPORT enrolment
Date: Monday, August 14, 2006 4:01:14 PM

Rose:

I think a call in may be sufficient if the relationship works well. We have decided to treat the weekends as regular working days and the nurses come in routinely. The RN also oversees all ongoing studies so is not wasting the time on a trip.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Phone: (205) 934 4680
FAX: (205) 934 3100
Email: wcarlo@peds.uab.edu

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Cc: Monica Collins
Subject: RE: SUPPORT enrolment

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Cc: 'Petrie, Carolyn'; Zaterka-Baxter, Kristin; Neil Finer
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Bethesda, MD 20892
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Rebecca Bara
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: sshankar@med.wayne.edu
Subject: SUPPORT questionnaire
Date: Tuesday, August 08, 2006 1:18:21 PM
Attachments: 8_1 SUPPORT Recruitment Strategy Questionnaire Ctr05.doc

---

Hi Rose,

Attached is Wayne's response to the SUPPORT Recruitment Questionnaire. I'm eager to hear from higher recruiting sites what seems to works for them.

Thanks,
Becky

SUPPORT Recruitment Strategy Questionnaire

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment.

1. Please check all of the individuals who obtain SUPPORT consent at your site:
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow __x only since the end of July
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator __x__
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe

2. Who obtains consent at night and on the weekends at your site?
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow __x only since the end of July
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator __x__
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe _____
   8. No one currently available _____

3. List the provisions you have made at your site for recruitment at night and on the weekends:
   1. On call research staff _____
   2. Clinical team obtains consent __x__ neonatal fellow, since the end of July
   3. Other _____

4. How many sites were included for potential recruitment of patients at your study center? ___1____
   How many sites are actively recruiting patients at your study center? __1___
   If the answers to questions posed in #4 are not identical, please provide an explanation:

5. Does OB/Perinatology requests consults on a 24/7 basis on mothers who present with threatened preterm delivery at 23-27 weeks gestational age?
   _x_ yes
   ___ no

List items that have enhanced recruitment at your site:

List items that have not helped recruitment that you anticipated would be helpful:

Please describe provisions you have made for this trial to insure recruitment 24 hours a day/7 days a week:

Since the end of July we have included neonatal fellows in the consent process at night and on weekends. Incentive for them will be funds for book purchase with consents obtained that result in enrolled babies.
For the research coordinator/research nurse who comes in on the weekend, an additional $ sum would be paid over the full-time salary.

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]; Kris Zaterka-Baxter; Petrie, Carolyn
Subject: Survey re: SUPPORT recruitment
Date: Tuesday, August 08, 2006 1:02:10 PM
Attachments: 8 1 SUPPORT Recruitment Strategy Questionnaire CTR19.doc

Apologies to you all, but I can't find the original email that tells who wanted this - so everyone receives it. Please note that a number of years ago here, we made the decision that parents deserved to have medically complex studies explained to them by a physician. In my role as coordinator, I usually talk to moms about SUPPORT participation after the initial discussion is conducted by the fellow and if he/she can't get back to answer questions and close the deal. We also made the decision to expect our fellows to help us recruit for our studies years ago as well.

Kathy J. Auten, 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

SUPPORT Recruitment Strategy Questionnaire - **Center 19 Duke**

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment.

1. Please check all of the individuals who obtain SUPPORT consent at your site:
   1. Attending on-service Neonatologist **YES**
   2. Neonatal fellow **YES**
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator **YES – to f/u preliminary discussions by MDs**
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) **YES**
   7. Other – please describe

2. Who obtains consent at night and on the weekends at your site?
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow **YES**
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator _____
   5. Other research staff _____
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe _____
   8. No one currently available _____

3. List the provisions you have made at your site for recruitment at night and on the weekends:
   1. On call research staff _____
   2. Clinical team obtains consent **YES** (can include attending, fellow, nurse practitioner)
   3. Other _____

4. How many sites were included for potential recruitment of patients at your study center? **1 – Duke Medical Center**
   How many sites are actively recruiting patients at your study center? **1 (only site that handles high risk deliveries)**

   If the answers to questions posed in #4 are not identical, please provide an explanation:

5. Does OB/Perinatology requests consults on a 24/7 basis on mothers who present with threatened preterm delivery at 23-27 weeks gestational age? **YES**

List items that have enhanced recruitment at your site: **Fellows are inhouse 24/7. Fellows are expected to assist in SUPPORT trial recruitment.**

List items that have not helped recruitment that you anticipated would be helpful: **N/A**

Please describe provisions you have made for this trial to insure recruitment 24 hours a day/7 days a week: **Fellows are inhouse 24/7, and research personnel are available to follow up with parents when fellows are unavailable.**

From: Monica Konstantino
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Petrie, Carolyn; Kris Zaterka-Baxter; Neil Finer
Subject: Re: support recruitment
Date: Monday, August 07, 2006 4:15:18 PM
Attachments: 8 1 SUPPORT Recruitment Strategy Questionnaire.doc

---

Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi:
>
> In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment. We are particularly interested in "successful strategies for recruitment" that have enhanced trial enrollment.
> please return the survey by Monday August 7.
>
> 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

Hello, we are sending along some of our strategies that we are using for support recruitment-
Monica

SUPPORT Recruitment Strategy Questionnaire

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment.

1. Please check all of the individuals who obtain SUPPORT consent at your site:
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow _____
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator X
   5. Other research staff X
   6. Off-service neonatologist (e.g. PI) X
   7. Other – please describe

2. Who obtains consent at night and on the weekends at your site?
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow X
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator X
   5. Other research staff X
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe _____
   8. No one currently available _____

3. List the provisions you have made at your site for recruitment at night and on the weekends:
   1. On call research staff X
   2. Clinical team obtains consent X (can include attending, fellow, nurse practitioner)
   3. Other _____

4. How many sites were included for potential recruitment of patients at your study center? 2
   How many sites are actively recruiting patients at your study center? 2
   If the answers to questions posed in #4 are not identical, please provide an explanation:

5. Does OB/Perinatology requests consults on a 24/7 basis on mothers who present with threatened preterm delivery at 23-27 weeks gestational age?
   X yes
   ___ no

List items that have enhanced recruitment at your site:

We give potential moms a brochure which explains the support the study in easier terms than the consent form.

After the initial consultation with the parents by the physician/PI, the follow-up visits are done by the research nurses.

List items that have not helped recruitment that you anticipated would be helpful:

Please describe provisions you have made for this trial to insure recruitment 24 hours a Day/7 days a week:

We screen the Labor and Delivery and Maternal Special Care Unit every morning and throughout the day as well as asking the triage nurse in the unit to notify us of any potential maternal admissions.

From: Kathy J Auten
To: Neil Finer
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Gantz, Marie
Subject: RE: Support infant
Date: Monday, August 07, 2006 3:47:28 PM

I will include it as an F5.

Kathy J. Auten, 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

"Neil Finer" <nfiner@ucsd.edu> wrote on 08/07/2006 03:40:24 PM:

> I would agree with filling in the form - however this was done for
> the infant's best interests and we should just note.
> Neil
>
>
> From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
> Sent: Monday, August 07, 2006 12:03 PM
> To: Neil Finer; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
> Cc: Kathy J Auten
> Subject: Support infant
>
> Hi,
> Duke has an infant [redacted] days into the support study. This infant was
> taken off the study oximeter by the treating physician for mod/sever
> dermatologic irritation where ever the oximeters probes were placed.
> Kathy said this was not due to the study oximeter as this infant
> reacts the same to clinical oximeters probes and is the nature of
> this infants skin. I talked to Abhik and he feels this should be
> reported as a protocol violation (taken off study oximeter early due
> to....) and not a withdrawal. Mom will continue to allow the use of
> previous data the collection of additional study related data. A
> Medwatch form should also be completed though AE not attributed to
> study. Wanted to be sure everyone was aware; please send any
> comments/suggestions.
> Thanks,
> Kris
>
>
> Kris Zaterka-Baxter, RN, CCRP
> RTI International
> 4426 South Miami Blvd.
> Durham, NC 27703
> Telephone: (919) 485-7750
> Fax: (919) 485-7762
> kzaterka@rti.org
>

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org; kzaterka@rti.org; mgantz@rti.org; nfiner@ucsd.edu
Subject: Re: Support infant
Date: Monday, August 07, 2006 3:46:25 PM

Currently on CV at a rate of 24, 20/6, MAP 8, 30%.

You will have the paperwork late today/early tomorrow.

Kathy J. Auten, 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 \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> wrote on 08/07/2006 03:34:03 PM:

> Is the infant still receiving oxygen? I would agree with Abhik -
> protocol violation/deviation
>
> Rose
> ---
> Sent from my BlackBerry Wireless Handheld
>
>
> ----- Original Message -----
> From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
> To: Neil Finer <nfiner@ucsd.edu>; Das, Abhik <adas@rti.org>;
> Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie <mgantz@rti.org>
> Cc: Kathy J Auten <auten002@mc.duke.edu>
> Sent: Mon Aug 07 15:03:03 2006
> Subject: Support infant
>
> Hi,
>
> Duke has an infant (b)(6) days into the support study. This infant was
> taken off the study oximeter by the treating physician for mod/sever
> dermatologic irritation where ever the oximeters probes were placed.
> Kathy said this was not due to the study oximeter as this infant
> reacts the same to clinical oximeters probes and is the nature of
> this infants skin. I talked to Abhik and he feels this should be
> reported as a protocol violation (taken off study oximeter early due
> to….) and not a withdrawal. Mom will continue to allow the use of
> previous data the collection of additional study related data. A
> Medwatch form should also be completed though AE not attributed to
> study. Wanted to be sure everyone was aware; please send any
> comments/suggestions.
>
> Thanks,
>
> Kris
>
>
>
>
>
> Kris Zaterka-Baxter, RN, CCRP
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> RTI International
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> Durham, NC 27703
>
> Telephone: (919) 485-7750
>
> Fax: (919) 485-7762
>
> kzaterka@rti.org
>
>
>

From:	Auman, Jeanette O.
To:	Angelita Hensman; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc:	Petrie, Carolyn; Zaterka-Baxter, Kristin; nxs5@cwru.edu; mbball@leland.stanford.edu; Pickett, James; Schaefer, Scott E.; Gantz, Marie; Perritt, Rebecca (Kitty); lucmille@iupui.edu; Kathy J Auten
Subject:	RE: Monthly report revisions(edition 1)08 03 06
Date:	Friday, August 04, 2006 11:49:43 PM
Attachments:	AnteRand.rtf

You mean like this? I added it before the July Steering Committee meeting; it will be included in this upcoming monthly report.

Jenny

-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Friday, August 04, 2006 5:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; nxs5@cwru.edu; mbball@leland.stanford.edu; Pickett, James; Schaefer, Scott E.; Auman, Jeanette O.; Gantz, Marie; Perritt, Rebecca (Kitty); lucmille@iupui.edu; Kathy J Auten
Subject: RE: Monthly report revisions(edition 1)08 03 06

Can we add a column for table 2.17D (pg 80 on the June report) to reflect the # of mothers enrolled in the main SUPPORT trial of those screened. Each center needs to have 50 mothers enrolled in the SUPPORT study (after the antenatal screening began) to stop enrollment for the secondary and we will need to keep track of this.
Thanks
Angelita

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 03, 2006 2:43 PM
To: Abbot Laptook; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; nxs5@cwru.edu; mbball@leland.stanford.edu; Angelita Hensman; Pickett, James; Schaefer, Scott E.; Auman, Jeanette O.; Gantz, Marie; Perritt, Rebecca (Kitty); lucmille@iupui.edu; Kathy J Auten
Subject: Monthly report revisions(edition 1)08 03 06

Hi,
The ad hoc monthly report revision committee met by teleconference.

Thanks to the group for all the helpful suggestions. The changes that will be made to the monthly report are attached.
Thanks
Rose
<<Monthly report revisions(edition 1)08 03 06.doc>>

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17D

Number of Mothers Enrolled in the Antenatal Consent Secondary Study
Status of Enrollment by Center

Clinical Center	Number Screened*	Number Approached**	Number of Consents Obtained***	Number Screened in Support	Number Randomized in Support
3:Case Western Univ.	10	8	4	6	4
4:Univ. of Texas (D)	11	11	9	8	5
5:Wayne State Univ.	.	.	.	.	.
8:Univ. of Miami	.	.	.	.	.
9:Emory University	44	40	20	26	13
11:Univ. of Cincinnati	29	27	7	20	3
12:Indiana Univ.	14	8	4	13	6
13:Yale University	30	23	12	22	2
14:Brown University	65	55	40	22	11
15:Stanford University	5	4	2	3	2
16:Univ. of Alabama	19	11	8	4	2
18:Univ. of Texas (H)	.	.	.	.	.
19:Duke University	60	51	20	32	15
20:Wake Forest	.	.	.	.	.
21:Children's (NY)	.	.	.	.	.
22:Univ. of Calif. at San Diego	14	12	4	7	6
	301	*250*	*130*	*163*	*69*

(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/14/06)

**** Number of unique screening IDs in the Ant01.***
***** Ant02 forms with Q. 1 = 'Y'.***
****** Number of consents obtained based on above criteria and ANT02 Q. 8 = 'Y'.***
Number Screened in Support - no. of SUPP01 forms with a DOB occurring AFTER the first DOB for each center on the ANT01 (used as an estimate protocol start date).
Number Randomized in Support - has a SUPP01 of above criteria and Q. D2 on SUPP02 = 'Y'.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Coding CPAP prongs with IMV settings
Date: Thursday, August 03, 2006 1:27:57 PM

FYI
Neil

From: Neil Finer
Sent: Thursday, August 03, 2006 10:27 AM
To: 'Zaterka-Baxter, Kristin'; Angelita Hensman at Brown
Cc: Wade Rich; Auman, Jeanette O.; alaptook@wihri.org; Nancy Newman; Wade Rich
Subject: RE: Coding CPAP prongs with IMV settings

Hi Angelita and Kris
I missed Angelita's email. I agree with this interpretation and non-invasive ventilation support is allowed after extubation for any infant in the trial.
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, August 03, 2006 8:46 AM
To: Angelita Hensman at Brown
Cc: Neil Finer; Wade Rich; Auman, Jeanette O.; alaptook@wihri.org; Nancy Newman
Subject: FW: Coding CPAP prongs with IMV settings

Hi,
If this is the new SiPAP, it should be coded as 3 = NSIMV per Michele Walsh during the SCM and will be added to Supp11 and 05 and the MOP. If this is not, please disregard.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, August 03, 2006 11:20 AM
To: Neil Finer
Cc: Wade Rich; Auman, Jeanette O.; Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook; nxs5@cwru.edu
Subject: Coding CPAP prongs with IMV settings

Hi Neil,

I thought we were done with all the SUPPORT study questions but here's one more..... our unit is using CPAP prongs (4cm) with IMV settings on some of our infants who need to be reintubated for apnea after 14 days of life. How should we code this on the SUPP11 form?

Thanks
Angelita

From:	Nancy Newman
To:	"Angelita Hensman"; "Neil Finer"
Cc:	"Wade Rich"; "Auman, Jeanette O."; Higgins, Rosemary (NIH/NICHD) [E]; "Abbot Laptook"; nxs5@cwru.edu
Subject:	RE: Coding CPAP prongs with IMV settings
Date:	Thursday, August 03, 2006 1:09:01 PM

It sounds to me like nasal SIMV.....NN

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Thursday, August 03, 2006 11:20 AM
To: Neil Finer
Cc: Wade Rich; Auman, Jeanette O.; Higgins, Rosemary (NIH/NICHD) [E]; Abbot Laptook; nxs5@cwru.edu
Subject: Coding CPAP prongs with IMV settings

Hi Neil,

I thought we were done with all the SUPPORT study questions but here's one more..... our unit is using CPAP prongs (4cm) with IMV settings on some of our infants who need to be reintubated for apnea after 14 days of life. How should we code this on the SUPP11 form?

Thanks
Angelita

From: Zaterka-Baxter, Kristin
To: eboger@wfubmc.edu
Cc: Nancy Peters; Furey, Anne; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support study oximeter transfer
Date: Tuesday, August 01, 2006 3:12:15 PM

Hi Erin,

I believe Nancy Peters discussed with you the possibility of transferring the Support study Masimo oximeters to another Network sites if needed while she's (b) (6) . We will need to have the following oximeters sent to Tufts University (address below). Please verify the following serial numbers and if possible, it would be great if you could send them either tomorrow or Thursday. If not, early next week will be fine too. Please let me know if you have any questions at all.
Thanks so much,
Kris

Serial Numbers	Color Codes
310834	ORANGE
310838	ORANGE
310874	ORANGE
310913	BLUE
310983	ORANGE
311139	ORANGE

Please send oximeters and docking stations to:
Anne Furey/Kieu-Nhi Pham
Division of Newborn Medicine
750 Washington Street, Tufts-NEMC #44
Boston, MA 02111
Phone: 617636-5322
Email: afurey@tufts-nemc.org

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:
Date: Tuesday, August 01, 2006 2:44:18 PM

Hi Rose
(b) (6)
Thanks for asking
Wade and I are heading to Stanford Friday to in-service Re SUPPORT. I have not heard from Albuquerque yet.
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 11:33 AM
To: Neil Finer
Subject: RE:

I want to have a list of potential opportunities to be used at sites that are not enrolling as well as Case Western.

I will keep you updated. (b) (6)

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 01, 2006 2:32 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:

Hi Rose
This is what it takes to enroll well.
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 11:03 AM
To: Nancy Newman
Cc: mcw3@cwru.edu; Neil Finer
Subject: RE:

Thanks
Neil – I will keep a running document of helpful comments like these!!
Rose

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, August 01, 2006 1:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu; 'Neil Finer'
Subject: RE:

Hi- we have worked with L&D this way in the past and we are up on Antepartum many times a week

reviewing maternal charts so we know most all the nurses. So I just approached each group and explained what we needed and also spoke to each floor's nurse supervisor to make them aware of what are plans were. The weekend calls are usually around 9A and 4P and more often is a patient's status is still being determined, but each area now 'expects" the calls on Sat and Sun.....NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 12:46 PM
To: Nancy Newman
Cc: mcw3@cwru.edu; Neil Finer
Subject: RE:

I like the research nurse calling the antepartum and L&D nurses on the weekends to look for potential study subjects. Prior to the trial starting, did you "in-service" or speak to the OB nursing staff in a formal way?? Or is this an informal arrangement that works at your site??

Thanks for responding so quick!!

Rose

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, August 01, 2006 12:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu
Subject: RE:

Hi Rose- here is the questionnaire.....NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 9:28 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu; Angelita Hensman; afurey@tufts-nemc.org; Becky bara; Bethany Ball; Cathy Grisby; Conra Backstrom; Ellen Hale; Georgia McDavid; karen-johnson@uiowa.edu; Kathy Auten; Lucy Miller; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; susan.tepper@hsc.utah.edu
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Neil Finer
Subject:

Hi:

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment. We are particularly interested in "successful strategies for recruitment" that have enhanced trial enrollment.
please return the survey by Monday August 7.

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]; Michele Walsh; Nancy Newman
Cc: mcw3@cwru.edu
Subject: RE: RE:
Date: Tuesday, August 01, 2006 2:33:24 PM

Sweet use of the language!!!!!!!!!!!!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 11:00 AM
To: Michele Walsh; Nancy Newman
Cc: mcw3@cwru.edu; Neil Finer
Subject: RE: RE:

This is helpful – we clearly need SUPPORT from all parties involved in the care of the moms and the babies.

Thanks
Rose

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, August 01, 2006 1:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Nancy Newman
Cc: mcw3@cwru.edu; Neil Finer
Subject: Re: RE:

Nancy met with the OB faculty and I spoke to the OB nursing leadership to advice them about the study. Nancy did fairly extensive inservices with the OB nurses to make them comfortable with the t piece resuscitator and the idea of cpap in the DR with tiny babes. It helped a great deal that we were part of the feasibility study.
Michele

> ----- Original Message -----
> **From:** Higgins, Rosemary (NIH/NICHD) [E]
> **To:** Nancy Newman
> **Cc:** mcw3@cwru.edu ; Neil Finer
> **Sent:** Tuesday, August 01, 2006 12:45 PM
> **Subject:** RE:
>
> I like the research nurse calling the antepartum and L&D nurses on the weekends to look for potential study subjects. Prior to the trial starting, did you "in-service" or speak to the OB nursing staff in a formal way?? Or is this an informal arrangement that works at your site??
>
> Thanks for responding so quick!!
>
> Rose
>
> ---
>
> **From:** Nancy Newman [mailto:nxs5@case.edu]
> **Sent:** Tuesday, August 01, 2006 12:42 PM
> **To:** Higgins, Rosemary (NIH/NICHD) [E]
> **Cc:** mcw3@cwru.edu
> **Subject:** RE:
>
> Hi Rose- here is the questionnaire.....NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 9:28 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu; Angelita Hensman; afurey@tufts-nemc.org; Becky bara; Bethany Ball; Cathy Grisby; Conra Backstrom; Ellen Hale; Georgia McDavid; karen-johnson@uiowa.edu; Kathy Auten; Lucy Miller; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; susan.tepper@hsc.utah.edu
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Neil Finer
Subject:

Hi:

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment. We are particularly interested in "successful strategies for recruitment" that have enhanced trial enrollment.
please return the survey by Monday August 7.

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: Nancy Newman
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@cwru.edu
Subject: RE:
Date: Tuesday, August 01, 2006 12:41:52 PM
Attachments: 8 1 SUPPORT Recruitment Strategy Questionnaire.doc

Hi Rose- here is the questionnaire.....NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 9:28 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu; Angelita Hensman; afurey@tufts-nemc.org; Becky bara; Bethany Ball; Cathy Grisby; Conra Backstrom; Ellen Hale; Georgia McDavid; karen-johnson@uiowa.edu; Kathy Auten; Lucy Miller; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; susan.tepper@hsc.utah.edu
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin; Neil Finer
Subject:

Hi:

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment. We are particularly interested in "successful strategies for recruitment" that have enhanced trial enrollment.
please return the survey by Monday August 7.

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
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

SUPPORT Recruitment Strategy Questionnaire

In an effort to maximize SUPPORT recruitment, we are obtaining information from you to share with the other sites. We would like you to list any and all strategies you are using for SUPPORT recruitment.

1. Please check all of the individuals who obtain SUPPORT consent at your site:
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow ___x_
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator ___x_
   5. Other research staff ___x_
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe

2. Who obtains consent at night and on the weekends at your site?
   1. Attending on-service Neonatologist _____
   2. Neonatal fellow __x__
   3. Neonatal nurse Practitioner _____
   4. Research Coordinator _____
   5. Other research staff __x__
   6. Off-service neonatologist (e.g. PI) _____
   7. Other – please describe _____
   8. No one currently available _____

3. List the provisions you have made at your site for recruitment at night and on the weekends:
   1. On call research staff __x___
   2. Clinical team obtains consent _____ (can include attending, fellow, nurse practitioner)

   3. Other __x- fellows in house available at night if necessary for consent when delivery emergent___

4. How many sites were included for potential recruitment of patients at your study center? ___1____
   How many sites are actively recruiting patients at your study center? __1___
   If the answers to questions posed in #4 are not identical, please provide an explanation:

5. Does OB/Perinatology requests consults on a 24/7 basis on mothers who present with threatened preterm delivery at 23-27 weeks gestational age?
   __x_ yes
   ___ no

List items that have enhanced recruitment at your site:
Total commitment from all attendings and fellows to support the SUPPORT! We also have arranged for the weekend research RN to call in to the labor and delivery and Antepartum floor charge nurses for new potential patients.

List items that have not helped recruitment that you anticipated would be helpful:
n/a

Please describe provisions you have made for this trial to insure recruitment 24 hours a day/7 days a week: Hired additional research staff (RN who covers weekends) along with assistance of the in house fellows-so that we can enroll at all times.

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie; Auman, Jeanette O.; Zaterka-Baxter, Kristin
Subject: RE: Steroid use-SUPPORT study
Date: Tuesday, August 01, 2006 11:18:11 AM

Rose:

It is definitely possible to do this. As far as I know, we have never had specifications provided to us for this type of edit.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 01, 2006 10:20 AM
To: Das, Abhik
Subject: FW: Steroid use-SUPPORT study

Abhik
We could write this in as a "check" correct?
Thanks
Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, August 01, 2006 10:15 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Angelita Hensman
Subject: FW: Steroid use-SUPPORT study

Neil,
Despite many conversations about this and other cross checks, to my knowledge RTI never looks between studies. All checks are intra-study only. Clearly the ability to do this type of cross-check on-the-fly instead of needing to wait until the trial is completed would be a tremendous asset to the Network.
Wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Tuesday, August 01, 2006 7:03 AM
To: Neil Finer
Cc: Auman, Jeanette O.; Pickett, James; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich; Abbot Laptook
Subject: RE: Steroid use-SUPPORT study

Hi Neil,

Thanks for the answer. We will put in the forms. One of our attending's used it on a couple of infants last month. Abbot has followed up on it and hopefully we will not see any more of this particular edit. The only way this violation will be noted in the database is if the sites put in a protocol violation form.

Does RTI cross check the GDB NG03 form as part of the SUPPORT edits? We do enter the "first date steroids were started for BPD/CLD" on the NG03 (B.5). An edit can be run if steroids were given before 21 days.

Angelita

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, July 31, 2006 6:25 PM
To: Angelita Hensman
Cc: Auman, Jeanette O.; Pickett, James; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: Steroid use-SUPPORT study

HI Angelita
Sorry for the delay in responding, we were in Salt Lake yesterday. Yes, this a violation. Don't feel bad as UCSD site leads in this category. In addition, we need to determine if the steroids were for lung disease. There is an increasing use for hypotension and you should provide a note if the indication was for hypotension.
I think we will need to look at this. So far there have been few of these violations noted.
Neil

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Friday, July 28, 2006 12:23 PM
To: Neil Finer
Cc: Auman, Jeanette O.; Pickett, James
Subject: Steroid use-SUPPORT study

Hi Neil,
Do we need to put in a protocol violation form if steroids are used prior to 21 days?
Thanks
Angelita

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Document2
Date: Monday, July 31, 2006 6:24:49 PM

Hi Rose
I would add to these questions whether Perinatal Consults are done 7/24 and if these are routine or require a specific request. We had a good visit with Salt Lake and I think that they are ready and should do well. They have an in-house Neonatologist 7/24 and this is going to help. The one issue that I would ask from my inquiries is when the NICU is informed about a new admission of pregnant women. My suggestion to Salt Lake is they develop a communication from the labor deck that informs the NICU within hours that there is a new admission of a woman from 23 to 27 weeks. From what I can determine, depending on notification from Perinatology may be ineffective.
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 28, 2006 6:40 AM
To: Das, Abhik; Neil Finer
Cc: Zaterka-Baxter, Kristin; Petrie, Carolyn
Subject: Document2

Hi,
Attached is a document requesting information from the sites about SUPPORT recruitment. I would like to find out what is working at sites with higher rates of recruitment in order to offer suggestion to sites where recruitment can be optimized. Please send me your thoughts and I will send it our to the Steering Committee.

Thanks for your help
Rose
<<Doc2.doc>>

From:	Zaterka-Baxter, Kristin
To:	kurt.schibler@cchmc.org
Cc:	Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	Support DSMB for GCRC
Date:	Friday, July 28, 2006 9:57:13 AM
Attachments:	NICHD NRN DSMC.doc DSMC Members [List 06.14.06].doc

Hi Dr. Schibler,
Please find attached Chapter 3 of the NICHD NRN Policies and Procedures. This chapter explains the NRN policies regarding the DSMC/B. The entire document can be found on the NRN web: https://neonatal.rti.org/private/pdf/Administration/PolicyNProcedures/NRN_PolicyProcedures.pdf . Also attached in the DSMC roster; please note the last 4 members listed are solely members for review of the Support Trial.

Please let me know if you have any questions,
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

Chapter 3

Committees

3.1 Data Safety and Monitoring Committee

Purpose

The purpose of the Data Safety and Monitoring Committee (DSMC) is to review and interpret protocols and study data in order to insure the safety of study subjects and to provide NICHD with advice on the progress of studies in the NICHD Neonatal Research Network.

Membership

The Data Safety and Monitoring Committee is appointed in accordance with established National Institute of Health (NIH) policies governing the use of advisors. The members are experts in neonatology, maternal fetal medicine, ethics, clinical trial design and biostatistics, and basic science, who are not participants in any way in the NICHD Neonatal Research Network. NICHD appoints the Chairman of the DSMC. The Director of the Center for Developmental Biology and Perinatal Medicine or designee, who is not a member of the Steering Committee, will serve as the executive secretary of the DSMC.

Responsibilities

The DSMC will meet regularly to review the protocols with respect to ethical and safety standards, monitor the safety of ongoing clinical trials, and advise on their conduct. It will report to the Director of NICHD and make recommendations if necessary. All data and deliberations of the DSMC will be strictly confidential. It may recommend protocol modifications based on concerns for patient welfare or scientific integrity. The committee will be privy to statistical data and case reports that it may require for its deliberations. It will review interim reports of patient accrual and outcome measures provided by the Data Center.

Each report will include tabulations and analyses by treatment group and clinical center by patient characteristics, and present all patients exits, mortality, and other major clinical

events. After reviewing each such report, the DSMC will assess the need to perform further in-depth evaluation of the benefits and risks of continuing the study. If it is determined that the study objectives have been satisfied based on data accrued to date, if patient safety would be compromised by continuation of the study, or if there are severe unanticipated problems with study conduct, the DSMC may recommend to the NICHD that the trial be terminated. The code of a masked study performed by the NICHD Neonatal Network will remain intact until the completion of the study, with the exception of interim review by the Data Safety and Monitoring Committee. Requests to restricted access to the study status, e.g. for the analysis of ancillary studies performed in individual centers, will not be honored if it might lead to premature disclosure of the results of the primary study. At the conclusion of individual studies, and at other times as may be deemed appropriate by the DSMC, the DSMC will recommend release of unmasked study data to the Steering Committee for analysis and publication in scientific journals.

The DSMC, under its Chairman, will prepare a written annual report for transmittal to NICHD. This report will summarize important findings of the studies undertaken by the Network and may include recommendations for protocol or procedural changes. In addition, the executive secretary will prepare brief minutes of each meeting and transmit appropriate information to the NICHD who will provide information to the Steering Committee. A report of each meeting will also be forwarded to the chairman of each participating institution's Investigational Review Board (IRB) and Principal Investigator.

NICHD Neonatal Research Network DSMC Membership Roster **06/14/06**

Gordon Avery, MD ***(DSMC Chair)***
Specialty: Neonatology, Clinical Trials
Telephone: (703) 820-3134
Cell: (703) 405(b) (6)
e-mail(b) (6)

Robert J. Boyle, MD
Specialty: Neonatology, Bioethics
Professor of Pediatrics
Dept. of Pediatrics,
Division of neonatology
Room 3747, Old Medical School
Hospital Drive
University of Virginia Health System
Charlottesville, VA 22908-0386
Telephone: (434) 924-5429
Fax: (434) 924-2816
e-mail: RJB6J@hscmail.mcc.virginia.edu

Christine A. Gleason, MD
Specialty: Neonatology, Cerebral-vascular Physiology
Department of Pediatrics
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Telephone: (206) 543-3200
Fax: (206) 543-8926
e-mail: cgleason@u.washington.edu

Marian Willinger, PhD
Specialty: Control of Breathing, SIDS
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Center for Developmental Biology and Perinatal Medicine
NICHD, NIH
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Michael G. Ross, M.D., M.P.H.
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Shrikant Bangdiwala , PhD
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University of North Carolina at Chapel Hill
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Chapel Hill, North Carolina 27514-4145
Phone: 919-962-3266
Fax: 919-962-3265
Email: kant@unc.edu

NICHD Neonatal Research Network Additional DSMC Members for the SUPPORT Trial

Carl Hunt, MD
Specialty: Neonatology, Sleep, Sleep Apnea
Director, National Center for Sleep Disorders Research
National Heart, Lung and Blood Institute
One Rockledge Centre Suite 6022 6705
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Bethesda, MD 20892-7933
Telephone: (301) 435-0199
Fax: (301) 480-3451
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Specialty: Neonatology, Respiratory Physiology
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Hammersmith Hospital,
Du Cane Road
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Fax: +44 208 764 8281
e-mail: merran.thomson@ic.ac.uk

Marilee C. Allen, MD
Specialty: Neonatology, High risk infant follow-up, Neurodevelopment
Associate Professor of Pediatrics
Department of Pediatrics/Division of Neonatology
The Johns Hopkins University School of Medicine
600 N. Wolfe St., CMSC 210
Baltimore MD 21287-3200
Telephone: (410) 955-4566
Fax: (410)955-0298
e-mail: mcallen@jhmi.edu

NICHD Neonatal Research Network Additional DSMC Members for the INOSITOL Trial

Lois Smith, MD
Specialty: Pediatric Ophthalmology
Harvard University Children's Hospital
300 Longwood Ave Fegan 4
Boston, MA 02115
Telephone: (617)919-2529
Fax: (617)730-0234
Email: lois.smith@childrens.harvard.edu

From: Neil Finer
To: Bradley Yoder
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Pt transfer in Support Study
Date: Wednesday, July 26, 2006 2:09:16 PM

Hi Brad
The first issue is whether the protocol is approved at the receiving hospital. If yes, then they can place a similar color device on the baby. Usually hospitals check in each unit through their BioMedical Engineering groups and I am not sure that they would want a device from another institution without some previous discussion. If no, then you should not continue the study till the infant returns to your facility or a study facility. If you have hospitals that frequently exchange infants I would ask whether they are OK with allowing the infant's Masimo to move with the infant. In any event, once taken off the unit should be downloaded and sent to RTI.
Hope this helps
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Wednesday, July 26, 2006 7:59 AM
To: Neil Finer
Cc: bpoindex@iupui.edu
Subject: Pt transfer in Support Study

What do you do when an infant is transferred from one of your SUPPORT study hospitals to another for surgical care?
Do you switch to a new Masimo (but same color code) at the new hospital.....or transfer the monitor with the infant from one hospital to the other?

Thanks for your response.

Brad Yoder

From: Das, Abhik
To: Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; neil finer; Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: SUPPORT secondary/coordinator call
Date: Tuesday, July 25, 2006 8:54:49 AM

Susan:

We could send sites queries both at enrollment+4 weeks and at 34 weeks PCA. Those who are waiting longer for recruitment could (a) indicate that they are doing so, or (b) we could perhaps exclude them from the first query. I have no problems with #3 and 4. I am copying Jenny on this email, but she is out this week; so you would likely hear from her next week.

Thanks

Abhik

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Monday, July 24, 2006 6:58 PM
To: Das, Abhik
Cc: higginsr@mail.nih.gov; neil finer; Zaterka-Baxter, Kristin
Subject: SUPPORT secondary/coordinator call

Hi all,

ABHIK - could you forward/share this with Jenny - I don't seem to have her email -

1) IS A "real time" TRACKING QUESTION POSSIBLE?? As you know, the original hope was that we would be able to break out part A of the MRI01, require that part to be completed by 4 weeks after enrollment, and get a more "real time" tracking of the secondary enrollment. The coordinators' call on Thursday 7/20 seemed to indicate that parents are being approached for consent for the Neuro secondary at a variety of different times during the course of hospitalization. Some sites with separate consents are waiting until 32 or 33 weeks to approach families. Thus, sending queries to those sites at enrollment + 4 weeks would not really be helpful, and might aggrevate some.

2) CONSIDER THIS?: Another potential option would be to break out the MRI01 part A, but wait to send a query to sites at 34 weeks PCA if they have not completed part A. This would not provide "real time" information (or even NEAR real time) but it could act as a reminder for sites to approach patients, get geared up for the MRI, basically put it on their radar screens. Do you think this would be helpful?

3) Jenny and Abhik - I would still like to put a gate question in the part B section (even though the early CUS is REQUIRED by the main protocol). I can send Jenny my thoughts on that - just forward her email address to me.

4) Getting the MRIs/CUS CDs - I believe Kristin has a log already for the CDs. Given the challenges outlined to me by Abhik in our last email correspondence about how we might "automatically" remind sites to get the CDs in, perhaps the best thing to do is just for me to have a conference call with Kristin every 3 months or so to compare the study completion vs. neuroimaging CD's "in" log. I could then draft emails to sites as reminders. This seems a bit

last century, but may be the best approach for the moment. Abhik, if you have other ideas how this might work better please let me know

Thanks

Susan

From: Zaterka-Baxter, Kristin
To: npeters@wfubmc.edu
Cc: auten002@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support Study oximeters
Date: Monday, July 24, 2006 12:21:41 PM

Hi Nancy,
Duke is in need of a few Support oximeters. They have a potential mom with multiples and are down to one blue oximeter. Would it be possible for you to send the following study oximeters with docking stations fed-ex, overnight, first morning delivery to Kathy at the address below?

310913 BLUE
310939 BLUE
310944 BLUE
310962 BLUE

Duke University Medical Center
Bell Bldg. Room 141
Bell Service Drive
Durham, NC 27710
Attn: Kathy Auten

I left a message on your phone as well. Please let me know either way so if this is not possible, I can contact another institution.

Thanks!
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
To: Michelle Tidwell; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Barbara Stoll; Ellen Hale; susie.buchter@oz.ped.emory.edu
Subject: RE: SUPPORT baby
Date: Monday, July 24, 2006 9:33:47 AM

Hi,
Please code this protocol deviation under the 'other' category and explain the circumstances. We currently don't have a code for the wrong card/GA group pulled but will add this option to form Supp06.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 24, 2006 9:16 AM
To: Michelle Tidwell; Zaterka-Baxter, Kristin
Cc: Das, Abhik; Barbara Stoll; Ellen Hale; susie.buchter@oz.ped.emory.edu
Subject: RE: SUPPORT baby

Hi,

This should be treated as a protocol violation (wrong card pulled) and an enrolled case (even those the infant expired).

Thanks

Rose

From: Michelle Tidwell [mailto:Michelle_Tidwell@oz.ped.emory.edu]
Sent: Monday, July 24, 2006 7:57 AM
To: kzaterka@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: SUPPORT baby

FYI. Please see the message below from Dr. Buchter regarding a SUPPORT baby, The baby's number will be (b) (6) Please let me know if I can be of further assistance. Thanks.

Michelle Tidwell, RN, BSN
Research Nurse
Neonatal Research Network

Emory University
(404) 616-5397 office (404) 899(b) pager

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

On (b) (6) at 25 3/7 weeks, I obtained antepartum consent from a mom for her baby to be enrolled in the SUPPORT trial. She delivered at (b) (6) making her 26 1/7 weeks.

Dr. Piazza and I wanted to notify you of two issues:
1. There was a protocol violation when the randomization card was pulled, it was for the lower gestation 24-25 6/7 weeks. The card was for early surfactant/orange. It was not noted until later that the card was of the wrong gestational age group. The randomization number was (b) (6)

2. The child was delivered acutely for loss of fetal heart tones and suspected abruption.
The 760- gram child was intubated in the DR and was given chest compressions and 2 doses of Epinephrine but died in the delivery room. He never stabilized long enough to receive surfactant, and he died at 27 minutes of age.

Ellen (b) (6) but will send the appropriate forms next week.

Susie Buchter

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Cc: Poole, W. Kenneth; Gantz, Marie
Subject: RE: Fwd: SUPPORT baby
Date: Monday, July 24, 2006 8:35:58 AM

That is what it sounds like to me.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, July 23, 2006 8:15 PM
To: Das, Abhik; Zaterka-Baxter, Kristin
Subject: Re: Fwd: SUPPORT baby

I think this should be a protocol violation and an enrollemnt based on
intent to treat - is this ok?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: 'adas@rti.org' <adas@rti.org>
Sent: Sun Jul 23 20:13:48 2006
Subject: Fw: Fwd: SUPPORT baby

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Susie Buchter <Susie.Buchter@oz.ped.emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Jul 22 18:46:14 2006
Subject: Fwd: SUPPORT baby

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

Saturday, July 22, 2006 6:44:05 PM Message
From: Susie Buchter
Subject: SUPPORT baby
To: rhiggins@mail.nih.gov
Cc: Ellen Hale
Michelle Tidwell
Barbara Stoll
Anthony Piazza

On (b) (6) at 25 3/7 weeks, I obtained antepartum consent from (b) (6) (b) (6) for her baby to be enrolled in the SUPPORT trial. She delivered at (b) (6), making her 26 1/7 weeks.

Dr. Piazza and I wanted to notify you of two issues:
1. There was a protocol violation when the randomization card was pulled, it was for the lower gestation 24-25 6/7 weeks. The card was for early surfactant/orange. It was not noted until later that the card was of the wrong gestational age group. The randomization number was 3087.

2. The child was delivered acutely for loss of fetal heart tones and suspected abruption.
The 760- gram child was intubated in the DR and was given chest compressions and 2 doses of Epinephrine but died in the delivery room. He never stabilized long enough to receive surfactant, and he died at 27 minutes of age.

Ellen (b) (6), but will send the appropriate forms next week.

Susie Buchter

From: Nancy Newman
To: "Barbara Stoll"
Cc: Higgins, Rosemary (NIH/NICHD) [E]; "Michele Walsh"; "Das, Abhik"; "Zaterka-Baxter, Kristin"; ellen_hale@oz.ped.emory.edu
Date: Friday, July 21, 2006 11:55:07 AM

Hi Barb and all-

Hope you got back to Atlanta timely. We actually sat on the runway for 3.r hrs before our plan was allowed to take off- weather somewhere. It made for a very long day.

I wanted to remind you about adding back the time of death to the GDB NGO3. Angelita pointed out that it was important from a tracking standpoint- i.e. to know whether to expect certain forms or information on forms (NGO3E, NGO7) or to determine eligibility for other studies (Candida, SUPPORT secondaries) or information (HUSs). I think she has a valid point.

Also, I had mentioned before about the ophthalmology and the lead in 'if yes' under question H.1. Conra asked aobut this several months ago. The 'If yes" should be after the question "was an exam performed for ROP" and not under part a. because part b.information is also included under 'if yes'. If NO you do not complete a. or b.

I hope this is clear. If not let me know. Thanks.....NN

From: Neil Finer
To: Zaterka-Baxter, Kristin; Gantz, Marie
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support Study forms revisions (Part 2)
Date: Thursday, July 20, 2006 2:30:35 PM

Hi Kris
I am OK with this as long as we have for that day an indication that the 21% is really 25%. I think that this may become an issue during the analysis so I would want to be able to do the analysis both ways, ie calling 25% RA and then running the actual FiO2m. I have a concern that while infants on room air spend significant time with SpO2 > 95% I am not sure that this is as true for infants at altitude receiving 25%.
This will be an additional analysis and we want to break out the infants on "RA" who are actually receiving 25%.
I will ask Marie to have a look at this as soon as we get some downloads from the 2 sites at altitude. I would want to know the time spent > 95% for the infants on 25% at altitude and see if this is similar to 21% at the other sites. We already have substantial data for the 21% exposure so we will know very quickly. If it turns out that the infants at 25% at altitude are different, we would want the actual FiO2 recorded.
The other approach is for the sites to enter the actual, ie 25%, and RTI to then convert the data for sites at altitude.
As you can see, I am concerned that 25% may not be equivalent relative to the occurrence of high SpO2s.
For now, I am OK with recording the actual for the 3 blood gases, and RA for the other 2 hour values for that day. This will also indicate that the intent was that these infants were meant to be on a RA equivalent.
Lets follow this as we get data.
Thanks
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, July 20, 2006 10:45 AM
To: Neil Finer
Cc: Das, Abhik; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support Study forms revisions (Part 2)

Thanks,
One question; Per Dr. Yoder, the mountain sites (NM and Utah) consider an adjusted Fi02 of < 25% to be equal to room air at sea level (21%). Should these sites document a 'Y' for 'on 02' only when ≥25% Fi02 for the q 2 hr measurements and record the actual (not adjusted) Fi02 with the 3 blood gas measurements which RTI will later adjust? Abhik does not see a problem with this approach but we need to know how you feel about this. If agreed, I can send out a memo and document this in the MOP.

Thanks,
Kris

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Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, July 20, 2006 10:28 AM

To: Zaterka-Baxter, Kristin
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support Study forms revisions (Part 2)

Hi Kris
We should continue to collect that FiO2 and the mode of support at the time of the blood gas. For the other q 2 hr queries (Sect Af) a notation of > 21% is adequate, and there is no need to indicate the mode of SUPPORT.
Thanks
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, July 19, 2006 2:46 PM
To: Nancy Newman; Neil Finer; Wade Rich; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Gantz, Marie; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: Support Study forms revisions (Part 2)

Part two:

I've added the Y/N instead of the dashes for Fi02 under the new 'on oxygen' column.
One more clarification. In the MOP we will clarify that the documented oximeter alarm checks should be recorded in the closest Scheduled Time slot as well.

Kris Zaterka-Baxter, RN, CCRP
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kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Wednesday, July 19, 2006 6:18 PM
To: 'Nancy Newman'; Neil Finer; 'Wade Rich'; 'mbball@leland.stanford.edu'; 'mcollins@peds.uab.edu'; Gantz, Marie; Das, Abhik
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Petrie, Carolyn
Subject: Support Study forms revisions

All,
Please find attached attempted draft revisions of the Supp05, Supp05A, Supp08 and new Supp12 (replacement oximeter form). Thank you all for your many suggestion on how to improve these form. Below are a few explanations about these revisions and a question or two:

Supp05:
We've split the blood gas data and the Fi02 data apart into two tables. This way you can record the Fi02 q2hrs and blood gasses TID closest to the scheduled times for each data point without too much confusion.
Questions:

1. We've changed the Fi02 data field to ask if the infant was 'On oxygen' during this time and footnoting 'on oxygen' means >21% Fi02 instead of asking the actual % Fi02 which may alleviate the possibility of recording two different Fi02 measurements, one in the Fi02 table, and one in the blood gas table, both potentially recorded for the same Scheduled Time slot. The question is if Neil, you feel this is sufficient data (on supplemental oxygen Y/N) or of you would prefer to have

the actual Fi02 %?

2. Do you want to collect mode of support (columns 'h', 'I', and 'j') q2hrs with the Fi02 data or TID with the blood gas data or with both sets of data?

We've added a code 9 to mode of support (column 'h'): 9= No Support all day and off study oximeter

Supp05A

We've revised the instructions on this form to clarify its intended use:
We've deleted **"if more than one"** intubation/extubation and added **"each time an"** intubation/extubation, and have deleted **"in the same day"**

Supp08

Marie Gantz and Neil Finer discussed the intended use of the Supp08 (AE) from during the subcommittee meeting. The data that is intended to be capture are any AEs within the first 14 days of life only. The statement "or prior to study status" will be removed from the instructions on the form and then clarified in the MOP

New Supp12

Given the potential need to record replacement study oximeters after 14 day, we've created a new form to capture all study oximeter replacements throughout the study period from initiation to 36 weeks or status. We've taken this question off the Supp05 form. Please note the original oximeter serial number is recorded on the Supp04 form. We had to call if Supp12 instead of the suggested Supp11(0) because this form will be used throughout the study and not just after the first 14 days.

I've not made any revisions to the MOP regarding these suggested draft revisions. Please review them. Please send any comments or suggestions. Once this small group has developed a more final draft, I can submit these changes to the subcommittee and upon approval to the larger group. Once agreed upon, I can make final revisions.
Thanks,
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To:	Nancy Newman; Neil Finer; Wade Rich; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Gantz, Marie; Das, Abhik
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject:	RE: Support Study forms revisions (Part 2)
Date:	Wednesday, July 19, 2006 6:45:45 PM
Attachments:	Supp05 Safety Monitor[07.19.06].doc

Part two:

I've added the Y/N instead of the dashes for Fi02 under the new 'on oxygen' column.
One more clarification. In the MOP we will clarify that the documented oximeter alarm checks should be recorded in the closest Scheduled Time slot as well.

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I've not made any revisions to the MOP regarding these suggested draft revisions. Please review them. Please send any comments or suggestions. Once this small group has developed a more final draft, I can submit these changes to the subcommittee and upon approval to the larger group. Once agreed upon, I can make final revisions.

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Rel 4.0
October 3, 2005
Revised March 7, 2006
Revised July 19, 2006

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ___

Complete a form each day through DOL 14

1. Study Day: __ __ 2. Date __ __ / __ __ / __ __ __ __

A. Record Fi02 and Respiratory Support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) *On Oxygen	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used	****(k) Oximeter Alarm Checks /=alarm checked and set per study limits
1. 02 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
2. 04 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
3. 06 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
4. 08 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
5. 10 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
6. 12 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
7. 14 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
8. 16 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
9. 18 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
10. 20 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
11. 22 : 00	__ __ : __ __	Y N	___	__.__ __	___	___
12. 23 : 59	__ __ : __ __	Y N	___	__.__ __	___	___

Record blood gas results closest to the Scheduled Time

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) * On Oxygen	(c) pH	(d) CO2	(e) PO2	*****(g) Source
1. 08 : 00	__ __ : __ __	Y N	__.__ __	__ __ __	__ __ __	___
2. 16 : 00	__ __ : __ __	Y N	__.__ __	__ __ __	__ __ __	___
3. 23 : 59	__ __ : __ __	Y N	__.__ __	__ __ __	__ __ __	___

15. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

*** On Supplemental Oxygen >21%**

**** Mode**
- 1= HFV
- 2= CV
- 3= Nasal SIMV/SiPAP
- 4= CPAP
- 5= NC
- 6= Hood
- 7= No Support
- 9= No Support all day and off study oximeter

***** CPAP Type**
- 1= Ventilator
- 4= Bubbles
- 6= Flow Driver
- 9= Other

****** Record Alarm Checks every six hours**

*******Source**
- 1= Arterial
- 2= Venous
- 3= Capillary

Initials of person completing this form: ___

From:	Zaterka-Baxter, Kristin
To:	Nancy Newman; Neil Finer; Wade Rich; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Gantz, Marie; Das, Abhik
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject:	Support Study forms revisions
Date:	Wednesday, July 19, 2006 6:18:25 PM
Attachments:	Supp05 Safety Monitor[07.19.06].doc SUPP05ASafetyMonitor[07.19.06(uc).doc SUPP08Adverse Event[07-19-06]Rev.doc SUPP12 oximeter replacement 07.16.06.doc

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NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Rel 4.0
October 3, 2005
Revised March 7, 2006
Revised July 16, 2006

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ___

Complete a form each day through DOL 14

1. Study Day: ___ 2. Date ___ / ___ / ____

A. Record Fi02 and Respiratory Support closest to the Scheduled Time.

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) *On Oxygen	(h)** Mode of Support	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used	****(k) Oximeter Alarm Checks /=alarm checked and set per study limits
1. 02 : 00	___ : ___	__.___	___	__.___	___	___
2. 04 : 00	___ : ___	__.___	___	__.___	___	___
3. 06 : 00	___ : ___	__.___	___	__.___	___	___
4. 08 : 00	___ : ___	__.___	___	__.___	___	___
5. 10 : 00	___ : ___	__.___	___	__.___	___	___
6. 12 : 00	___ : ___	__.___	___	__.___	___	___
7. 14 : 00	___ : ___	__.___	___	__.___	___	___
8. 16 : 00	___ : ___	__.___	___	__.___	___	___
9. 18 : 00	___ : ___	__.___	___	__.___	___	___
10. 20 : 00	___ : ___	__.___	___	__.___	___	___
11. 22 : 00	___ : ___	__.___	___	__.___	___	___
12. 23 : 59	___ : ___	__.___	___	__.___	___	___

Record blood gas results closest to the Scheduled Time

(a) Scheduled Time	(b) Time Measured (hour : min)	(f) * On Oxygen	(c) pH	(d) CO2	(e) PO2	*****(g) Source
1. 08 : 00	___ : ___	__.___	_.__	___	___	___
2. 16 : 00	___ : ___	__.___	_.__	___	___	___
3. 23 : 59	___ : ___	__.___	_.__	___	___	___

15. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

*** On Supplemental Oxygen >21%**

**** Mode**
1= HFV
2=CV
3= Nasal SIMV/SiPAP
4= CPAP
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6=Hood
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9= No Support all day and off study oximeter

***** CPAP Type**
1= Ventilator
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****** Record Alarm Checks every six hours**

*******Source**
1= Arterial
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Initials of person completing this form: ___

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPPORT Version 3.0
Revised June 5, 2006
Revised July 19, 2006

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

This form should be completed each time an intubation/extubation occurs ~~in the same day.~~

Report No __ __

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

C.

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 __ __ __
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      6. Sepsis/R/O Sepsis? Y N
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      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: __ __ __

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: __ __ __

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Replacement Oximeter Form

Center: __ __ Site: ___ Network No. __ __ __ __ Birth No. ___ Mother's Initials: __ __ __

Complete this form each time a replacement study oximeter is used.

a. Episode Number	b. Date Oximeter Replaced Month / Day / Year	c. Time Oximeter Replaced Hr : Min	d. Replacement Oximeter Serial Number	e. Replacement Oximeter Color Code 1= Blue 2 = Orange
1.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
2.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
3.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
4.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
5.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
6.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
7.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
8.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
9.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___
10.	__ __ / __ __ / __ __ __ __	__ __ : __ __	__ __ __ __ __ __	___

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Date: Monday, July 17, 2006 11:09:43 PM

Hi Rose
I will put together some minutes for today's meeting.
We have an EXIT procedure early in the AM for an infant with CHAOS – I will not be able to call in. I trust Wally will summarize our discussions.
I share with you frustrations regarding enrollments with at least 3 centers with < 5 infants and the decisions not to do MR's in spite of available payments is disappointing.
I was shocked to hear about complaints with capitation for SUPPORT – This study is well funded in addition to the base costs provided, and the most difficult part is the consent.
I will continue to try to get this trial completed, but I question the motivation of some of the players.
Keep up the good fight, I have a few of my own.
Be well
Neil

From:	Neil Finer
To:	Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc:	Zaterka-Baxter, Kristin (b) (6) msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject:	RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date:	Monday, July 17, 2006 11:42:39 AM
Attachments:	Pct in range since March (supp O2) 7-17-06.rtf Pct in range since March (room air) 7-17-06.rtf

TIS ME, YET AGAIN
Marie made these graphs to show the narrow target range.
She will bring copies to the meeting
Neil

From: Neil Finer
Sent: Monday, July 17, 2006 6:39 AM
To: Neil Finer; 'Petrie, Carolyn'; 'wcarlo@peds.uab.edu'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Poole, W. Kenneth'; 'nxs5@cwru.edu'; Wade Rich; 'Gantz, Marie'
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Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

The previous room air was only the shortcut- Here is the actual Table – I hope.
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From: Neil Finer
Sent: Monday, July 17, 2006 5:23 AM
To: Neil Finer; 'Petrie, Carolyn'; 'wcarlo@peds.uab.edu'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Poole, W. Kenneth'; 'nxs5@cwru.edu'; Wade Rich; 'Gantz, Marie'
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Hi
I think I sent you 2 of the same tables. The Room Air Total describes the time in room air, whereas the total represents time in oxygen.
Sorry for any confusion.
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To: Neil Finer; 'Petrie, Carolyn'; 'wcarlo@peds.uab.edu'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Poole, W. Kenneth'; 'nxs5@cwru.edu'; Wade Rich; 'Gantz, Marie'
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in Oxygen.
I have asked Marie to provide data for the narrow target – 88% to 92%.
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Cc: 'Zaterka-Baxter, Kristin'[(b) (6) redacted]; 'msumner@peds.uab.edu'; Fernando Martinez; 'bvecchio@careNE.org'; 'Webb, Robin E.'; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone
Here is some new information regarding the consent process for SUPPORT. We will briefly discuss during Monday's meeting.
Be well
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PERCENT OF TIME SPENT IN EACH OXIMETER DISPLAY RANGE SINCE 3/15/06
HOURS ON SUPPLEMENTAL 02 ONLY
(DATA RECEIVED AS OF 7/14/2006)

		Percent of time in each O2 range		
Infants	Hours	<84	84-96	>96
32	4850	7.3	81.6	11.1

		Percent of time in each O2 range		
Infants	Hours	<85	85-95	>95
32	4850	8.1	77.5	14.3

		Percent of time in each O2 range		
Infants	Hours	<88	88-92	>92
32	4850	18.8	41.5	39.7

PERCENT OF TIME SPENT IN EACH OXIMETER DISPLAY RANGE SINCE 3/15/06
HOURS IN ROOM AIR ONLY
(DATA RECEIVED AS OF 7/14/2006)

Infants	Hours	Percent of time in each O2 range <84	84-96	>96
31	4599	2.2	51.8	46.0

Infants	Hours	Percent of time in each O2 range <85	85-95	>95
31	4599	2.5	46.7	50.8

Infants	Hours	Percent of time in each O2 range <88	88-92	>92
31	4599	5.2	19.3	75.5

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To:	Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
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Subject:	RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date:	Monday, July 17, 2006 9:39:13 AM
Attachments:	Pct in range since March (room air total) 7-14-06.rtf

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		<85	85-95	>95
31	4599	2.5	46.7	50.8

From:	Neil Finer
To:	Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc:	Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject:	RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date:	Monday, July 17, 2006 9:24:46 AM
Attachments:	~$t in range since March (room air total) 7-14-06.rtf Pct in range since March (total) 7-14-06.rtf

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Cc: 'Zaterka-Baxter, Kristin'(b) (6) '; 'msumner@peds.uab.edu'; Fernando Martinez; 'bvecchio@careNE.org'; 'Webb, Robin E.'; Wade Rich
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Infants	Hours	Percent of time in each O2 range		
		<85	85-95	>95
31	4599	2.5	46.7	50.8

PERCENT OF TIME SPENT IN EACH OXIMETER DISPLAY RANGE SINCE 3/15/06
HOURS ON SUPPLEMENTAL 02 ONLY
(DATA RECEIVED AS OF 7/14/2006)

Infants	Hours	Percent of time in each O2 range		
		<84	84-96	>96
32	4850	7.3	81.6	11.1

Infants	Hours	Percent of time in each O2 range		
		<85	85-95	>95
32	4850	8.1	77.5	14.3

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: (b) (6)
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Monday, July 17, 2006 9:19:00 AM
Attachments: Pct in range since March (room air total) 7-14-06.rtf
Pct in range since March (total) 7-14-06.rtf

Sorry Rose
Our server was down for the weekend.
Here are the 2 tables.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, July 16, 2006 11:39 AM
To: Neil Finer
Cc(b) (6)
Subject: Re: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil
I am only able to pull up one table tited "percent of time spent in each oximeter display range sine 3/15/06 hour on supplemental oxygen." Both tables have the same data - can you resend and I can have both available tomorrow. Also, please copy to our home email (b) (6) as I am having trouble accessing the nih server from home today.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Neil Finer <nfiner@ucsd.edu>
To: Neil Finer <nfiner@ucsd.edu>; Petrie, Carolyn <petrie@rti.org>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Michele Walsh <mcw3@case.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger Faix <Roger.Faix@hsc.utah.edu>; alaptook@WIHRI.org <alaptook@WIHRI.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>; Poole, W. Kenneth <poo@rti.org>; nxs5@cwru.edu <nxs5@cwru.edu>; Wade Rich <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>(b) (6)
(b) (6); msumner@peds.uab.edu <msumner@peds.uab.edu>; Fernando Martinez <fmartinez@ucsd.edu>; bvecchio@careNE.org <bvecchio@careNE.org>; Webb, Robin E. <rwebb@rti.org>; Wade Rich <wrich@ucsd.edu>
Sent: Fri Jul 14 18:58:51 2006
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

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From: Zaterka-Baxter, Kristin
To: Auman, Jeanette O.; Wade Rich
Cc: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Number of antenatal consent forms from each site.
Date: Sunday, July 16, 2006 8:56:54 AM

Hi,
It was also suggested by Ellen Hale that we add a 'serial number' field on the Supp11 as a check and to capture any change in oximeters after 14 days. We can discuss this at the SCM or after, which ever you prefer.
Thanks,
Kris

From: Auman, Jeanette O.
Sent: Fri 7/14/2006 11:35 AM
To: 'Wade Rich'; Zaterka-Baxter, Kristin
Cc: Neil Finer; higginsr@mail.nih.gov
Subject: RE: Number of antenatal consent forms from each site.

We're adding the color check to the batch edits, Ken and Marie had recently suggested it.

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Friday, July 14, 2006 11:31 AM
To: Zaterka-Baxter, Kristin
Cc: Auman, Jeanette O.; Neil Finer; higginsr@mail.nih.gov
Subject: FW: Number of antenatal consent forms from each site.

Kris,
During a conversation about SUPPORT with Angelita re: how to document a new oximeter serial # for kids who have a machine replaced AFTER 14 days, it occurred to me that we do not have a clue if people are using the correct color device on their original setup. Is it possible to:

1) Do a data check against the list to make sure that the serial # entered on the admission form is the same color as the randomization code?
2) Come up with a plan for how to document a changed device after 14 days, and make sure it too is of the the appropriate color ?

Wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Friday, July 14, 2006 7:36 AM
To: Wade Rich
Subject: RE: Number of antenatal consent forms from each site.

Wade: I am here all day and should be in my office most of the day except between 12 and 2pm. Give me a call when you have time.
Angelita

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 13, 2006 9:40 AM
To: Angelita Hensman
Cc: Neil Finer
Subject: RE: Number of antenatal consent forms from each site.

Angelita,

Looks like someone was busy in June. 7 kids ! Nice work. Would love to talk to you about
1) Screening
2) New forms when volume is high.

wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Monday, June 05, 2006 10:27 AM
To: 'Zaterka-Baxter, Kristin'
Cc: Wade Rich; 'auten002@mc.duke.edu'
Subject: RE: Number of antenatal consent forms from each site.

We are not close to 50 moms who delivered in the window yet so no rush. Can be discussed at the next subcommittee meeting in July.
Thanks
Angelita

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, June 05, 2006 1:08 PM
To: wrich@ucsd.edu; wrich@ucsd.edu; Angelita Hensman
Cc: Das, Abhik; auten002@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: Number of antenatal consent forms from each site.

Hi,

I've discussed this with Abhik and Rose. The consensus was that if you would like to have accrual continue beyond the stated 50 mother's who deliver with in the study window per center; it needs a subcommittee discussion/vote and a formal revision if agreed upon. Until this can happen, Angelita, if you have achieved the study accrual goal per site, you should temporarily hold any further accrual until a final subcommittee decision has been made. Please let me know if we should try to put together a conference call to discuss this or any other thoughts or comments.

Thanks again,

Kris

Kris Zaterka-Baxter

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (191) 485-7762

kzaterka@rti.org

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Monday, June 05, 2006 12:36 PM
To: Zaterka-Baxter, Kristin; wrich@ucsd.edu
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

I do know what the protocol states. That was not my question.

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, June 05, 2006 12:25 PM
To: wrich@ucsd.edu; Angelita Hensman
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

Hi,

The protocol states "fifty mothers who have delivered within the window at each center" (page 3 Design and Methods). If all forms collected resulted in delivery within the window, data collection should stop per protocol. There is no protocol deviation recorded if collecting data beyond what was initially stated but I'm not sure it there are any other implications.

Thanks,

Kris

RTI International

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Durham, NC 27703

Telephone: (919) 485-7750

Fax: (191) 485-7762

kzaterka@rti.org

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Sent: Monday, June 05, 2006 12:13 PM
To: 'Angelita Hensman'; Zaterka-Baxter, Kristin
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

Because many centers will be lagging on this, my take is we should continue to gather them. Will let the rest of the group weigh in.

wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Monday, June 05, 2006 8:52 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik; auten002@mc.duke.edu; wrich@ucsd.edu
Subject: Number of antenatal consent forms from each site.

Hi Kris,

Do we stop at 50 antenatal forms from our site or do we need to keep going?

Thanks

Angelita

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(DATA RECEIVED AS OF 7/14/2006)

Infants	Hours	Percent of time in each O2 range		
		<84	84-96	>96
32	4850	7.3	81.6	11.1

Infants	Hours	Percent of time in each O2 range		
		<85	85-95	>95
32	4850	8.1	77.5	14.3

PERCENT OF TIME SPENT IN EACH OXIMETER DISPLAY RANGE SINCE 3/15/06
HOURS ON SUPPLEMENTAL 02 ONLY
(DATA RECEIVED AS OF 7/14/2006)

Infants	Hours	Percent of time in each O2 range		
		<84	84-96	>96
32	4850	7.3	81.6	11.1

Infants	Hours	Percent of time in each O2 range		
		<85	85-95	>95
32	4850	8.1	77.5	14.3

From: Wade Rich
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Friday, July 14, 2006 3:09:54 PM

Support Subcommittee:
We would also like to discuss the addition of a data point on Supp11 that will allow us to do an error check on oximeter serial #s to make sure the right color is
being used based on the randomization. Currently the serial # is only documented at the beginning of the study, and for any changes in the first 14 days. We need to add the ability to put in a new serial number later if a child is restarted on a different oxim than the one he had initially. Additionally, both of these numbers will now be checked against the oximeter database and compared to the randomization for that child to be certain the color code of the oximeter matches the color code of the randomization.
Thanks,
Wade

From: Neil Finer
Sent: Friday, July 14, 2006 12;03 PM
To: Neil Finer; 'Petrie, Carolyn'; 'wcarlo@peds.uab.edu'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Poole, W. Kenneth'; 'nxs5@cwru.edu'; Wade Rich; 'Gantz, Marie'
Cc: 'Zaterka-Baxter, Kristin'; (b) (6) '; 'msumner@peds.uab.edu'; Fernando Martinez; 'bvecchio@careNE.org'; 'Webb, Robin E.'; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone
Here is some new information regarding the consent process for SUPPORT. We will briefly discuss during Monday's meeting.
Be well
Neil

From: Neil Finer
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Friday, July 14, 2006 3:03:14 PM
Attachments: AnteRand (2).rtf

Hello Everyone
Here is some new information regarding the consent process for SUPPORT. We will briefly discuss during Monday's meeting.
Be well
Neil

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17D

Number of Mothers Enrolled in the Antenatal Consent Secondary Study
Status of Enrollment by Center

Clinical Center	Number Screened*	Number Approached**	Number of Consents Obtained***	Number Screened in Support	Number Randomized in Support
3:Case Western Univ.	10	8	4	6	4
4:Univ. of Texas (D)	11	11	9	8	5
5:Wayne State Univ.	.	.	.	.	.
8:Univ. of Miami	.	.	.	.	.
9:Emory University	44	40	20	26	13
11:Univ. of Cincinnati	29	27	7	20	3
12:Indiana Univ.	14	8	4	13	6
13:Yale University	30	23	12	22	2
14:Brown University	65	55	40	22	11
15:Stanford University	5	4	2	3	2
16:Univ. of Alabama	19	11	8	4	2
18:Univ. of Texas (H)	.	.	.	.	.
19:Duke University	60	51	20	32	15
20:Wake Forest	.	.	.	.	.
21:Children's (NY)	.	.	.	.	.
22:Univ. of Calif. at San Diego	14	12	4	7	6
	301	*250*	*130*	*163*	*69*

(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/14/06)

**** Number of unique screening IDs in the Ant01.***
***** Ant02 forms with Q. 1 = 'Y'.***
****** Number of consents obtained based on above criteria and ANT02 Q. 8 = 'Y'.***
Number Screened in Support - no. of SUPP01 forms with a DOB occurring AFTER the first DOB for each center on the ANT01 (used as an estimate protocol start date).
Number Randomized in Support - has a SUPP01 of above criteria and Q. D2 on SUPP02 = 'Y'.

From: Wade Rich
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin
Cc: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Number of antenatal consent forms from each site.
Date: Friday, July 14, 2006 12:07:37 PM

I think it is needed. Please check with the subcommittee before changing it.

wade

From: Auman, Jeanette O. [mailto:joa@rti.org]
Sent: Friday, July 14, 2006 8:48 AM
To: Wade Rich; Zaterka-Baxter, Kristin
Cc: Neil Finer; higginsr@mail.nih.gov
Subject: RE: Number of antenatal consent forms from each site.

The only other form completed after day 14, is the SUPP11, correct? Could we put an additional question on that form asking something like, 'If a replacement oximeter was placed that day?' and 'If yes, serial number?'

Then we could check the serial number to the color code in the batch edits as I'm going to do for the other serial numbers on Supp04 & Supp05.
Jenny

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Friday, July 14, 2006 11:39 AM
To: Auman, Jeanette O.; Zaterka-Baxter, Kristin
Cc: Neil Finer; higginsr@mail.nih.gov
Subject: RE: Number of antenatal consent forms from each site.

> Ken is ahead of me as usual. Any thoughts on the late oximeter changes?
> wade
>
> ---
>
> **From:** Auman, Jeanette O. [mailto:joa@rti.org]
> **Sent:** Friday, July 14, 2006 8:35 AM
> **To:** Wade Rich; Zaterka-Baxter, Kristin
> **Cc:** Neil Finer; higginsr@mail.nih.gov
> **Subject:** RE: Number of antenatal consent forms from each site.
>
> We're adding the color check to the batch edits, Ken and Marie had recently suggested it.
>
> > -----Original Message-----
> > **From:** Wade Rich [mailto:wrich@ucsd.edu]
> > **Sent:** Friday, July 14, 2006 11:31 AM
> > **To:** Zaterka-Baxter, Kristin
> > **Cc:** Auman, Jeanette O.; Neil Finer; higginsr@mail.nih.gov
> > **Subject:** FW: Number of antenatal consent forms from each site.
> >
> > Kris,
> > During a conversation about SUPPORT with Angelita re: how to document a new oximeter serial # for kids who have a machine replaced AFTER 14 days, it occurred to me that we do not have a clue if people are using the correct color device on their original setup. Is it possible to:

1) Do a data check against the list to make sure that the serial # entered on the admission form is the same color as the randomization code?
2) Come up with a plan for how to document a changed device after 14 days, and make sure it too is of the the appropriate color ?

Wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Friday, July 14, 2006 7:36 AM
To: Wade Rich
Subject: RE: Number of antenatal consent forms from each site.

Wade: I am here all day and should be in my office most of the day except between 12 and 2pm. Give me a call when you have time.
Angelita

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 13, 2006 9:40 AM
To: Angelita Hensman
Cc: Neil Finer
Subject: RE: Number of antenatal consent forms from each site.

Angelita,

Looks like someone was busy in June. 7 kids ! Nice work. Would love to talk to you about
1) Screening
2) New forms when volume is high.

wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Monday, June 05, 2006 10:27 AM
To: 'Zaterka-Baxter, Kristin'
Cc: Wade Rich; 'auten002@mc.duke.edu'
Subject: RE: Number of antenatal consent forms from each site.

We are not close to 50 moms who delivered in the window yet so no rush. Can be discussed at the next subcommittee meeting in July.
Thanks
Angelita

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, June 05, 2006 1:08 PM
To: wrich@ucsd.edu; wrich@ucsd.edu; Angelita Hensman
Cc: Das, Abhik; auten002@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject: RE: Number of antenatal consent forms from each site.

Hi,

I've discussed this with Abhik and Rose. The consensus was that if you would like to have accrual continue beyond the stated 50 mother's who deliver with in the study window per center; it needs a subcommittee discussion/vote and a formal revision if agreed upon. Until this can happen, Angelita, if you have achieved the study accrual goal per site, you should temporarily hold any further accrual until a final subcommittee decision has been made. Please let me know if we should try to put together a conference call to discuss this or any other thoughts or comments.
Thanks again,
Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Monday, June 05, 2006 12:36 PM
To: Zaterka-Baxter, Kristin; wrich@ucsd.edu
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

I do know what the protocol states. That was not my question.

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, June 05, 2006 12:25 PM
To: wrich@ucsd.edu; Angelita Hensman
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

Hi,
The protocol states "fifty mothers who have delivered within the window at each center" (page 3 Design and Methods). If all forms collected resulted in delivery within the window, data collection should stop per protocol. There is no protocol deviation recorded if collecting data beyond what was initially stated but I'm not sure it there are any other implications.

Thanks,
Kris

RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Monday, June 05, 2006 12:13 PM
To: 'Angelita Hensman'; Zaterka-Baxter, Kristin
Cc: Das, Abhik; auten002@mc.duke.edu
Subject: RE: Number of antenatal consent forms from each site.

Because many centers will be lagging on this, my take is we should continue to gather

them. Will let
the rest of the group weigh in.
wade

From: Angelita Hensman [mailto:AHensman@wihri.org]
Sent: Monday, June 05, 2006 8:52 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik; auten002@mc.duke.edu; wrich@ucsd.edu
Subject: Number of antenatal consent forms from each site.

Hi Kris,
Do we stop at 50 antenatal forms from our site or do we need to keep going?
Thanks
Angelita

From: Petrie, Carolyn
To: nfiner@ucsd.edu; srhintz@stanford.edu; Navarrete, Cristina; Duara, Shahnaz; Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn
Subject: SUPPORT Subcommittee meeting
Date: Friday, July 14, 2006 10:36:33 AM

Dear All-

Please join us for the SUPPORT subcommittee meeting Monday, July 17th from 5:00-6:00pm ET via conference call.

To join the call,

Dial Toll Free, 866-675(b) (6)
Passcode: (b) (6)

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: Zaterka-Baxter, Kristin
To: mcollins@peds.uab.edu
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN Masimo Oximeters
Date: Thursday, July 13, 2006 4:17:49 PM

Hi,
Below are the color coded treatment assignments for the 10 Masimo oximeters sent to you yesterday.

Please let me know if you have any questions.
Thanks again,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Chris Novak [mailto:CNovak@masimo.com]
Sent: Wednesday, July 12, 2006 4:59 PM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Masimo Oximeters

Kris,
Here are the assignments for this shipment.

330369 - Orange
333642 - Blue
333576 - Blue
330392 - Orange
330307 - Orange
330096 - Blue
333581 - Blue
333647 - Blue
330458 - Orange
333658 - Orange

Chris

From: Zaterka-Baxter, Kristin
To: mcollins@peds.uab.edu
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN Masimo Oximeters
Date: Thursday, July 13, 2006 4:11:29 PM

Hi Monica,
The color coded treatment assignments for the first shipment of 10 oximeters is below (these are the code that went missing for a while). For the shipment sent yesterday, I will send another email with those assignments. I've asked Masimo if we should keep all 20 oximeters or send a few back and am waiting for a reply.
Thanks for your patience!

Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Chris Novak [mailto:CNovak@masimo.com]
Sent: Thursday, July 13, 2006 2:34 PM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Masimo Oximeters

Kris,
We were able to locate the serial number designation for the units that you presently have. I have attached them below:

Sorry for the delay,
Chris

329709 - Orange	329083 - Blue
329689 - Orange	328935 - Blue
329713 - Orange	329207 - Blue
329703 - Orange	328981 - Blue
329706 - Orange	329168 - Blue

Docking Station:
074732
074768
073615
079445
074743
077619
075185
073643
079567
074766

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; carl_dangio@urmc.rochester.edu; Cassandra_Horihan@URMC.Rochester.edu; JANET.MORGAN@childrens.com; Ang, Jocelyn Y; Mperalta@peds.uab.edu; RSchelonka@peds.uab.edu; Roy.Heyne@utsouthwestern.edu; theresa_murray@urmc.rochester.edu; vphillips@peds.uab.edu; danny.benjamin@duke.edu; Dhiren H. Desaiu; Brenda.H.Morris@uth.tmc.edu; liwashbu@wfubmc.edu; ronnie_guillet@urmc.rochester.edu; vanmeurs@leland.stanford.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; 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; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson; Frantz, Ivan; Furey, Anne; Pablo.Sanchez@UTSouthwestern.edu; kurt.schibler@cchmc.org; Michael Cotten; Bell, Edward; Johnson, Karen; Kristi Watterberg; papile@unm.edu; Roger Faix; Susan Tepper; Conra Backstrom; bradley.yoder@hsc.utah.edu; Walid.Salhab@UTSouthwestern.edu; aaf2@po.cwru.edu; ira_adams-chapman@oz.ped.emory.edu; cbauer@peds.med.miami.edu; apappas@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; steichjl@email.uc.edu; (b) (6) Mayes, Linda; maegan.c.currence@uth.tmc.edu; SEguaras@med.miami.edu; MNeri@med.miami.edu; mgfuller@ucsd.edu; lnoel@wihri.org; ldrichar@iupui.edu; diane_hust@urmc.rochester.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; Jackie.Hickman@Childrens.com; bss5@cwru.edu; lohme001@mc.duke.edu; Stevens, Timothy; Charles.Green@uth.tmc.edu; Patricia.W.Evans@uth.tmc.edu; Kimberly.Yolton@cchmc.org

Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Newman, Jamie; Petrie, Carolyn; Brinkley, Margo F.; Poole, W. Kenneth; Auman, Jeanette O.; Schaefer, Scott E.; Price, Jeffrey M.; Medeiros, Donna J.

Subject: RE: June 2006 NRN Monthly Report

Date: Thursday, July 13, 2006 8:25:33 AM

Attachments: Report30JUN2006.pdf

Hi all,

Please find attached the NRN monthly report for June 2006. In this report we have included tables for the aEEG F/U study and the ROP tracking for Support. Please note the monthly report will be available on the NRN web https://neonatal.rti.org later today.

Thanks and please let me know if you have any questions.

Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

NICHD NEONATAL RESEARCH NETWORK

MONTHLY REPORT FOR THE PERIOD ENDING

June 30, 2006

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CHAPTER ONE

Missing Forms, Follow-up Compliance, and Follow-up Certifications

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.1

Summary of Missing GDB Forms
By Form Type and Center

	Clinical Center																	
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
NF00-Screening Log	3	4	.	5	2	17	1	1	.	.	.	2	12	2	.	1	.	50
NG01-Screening Log	.	.	.	1	.	2	.	.	.	.	.	.	.	.	.	.	.	3
NG02-Baseline	1	.	5	2	.	15	7	6	.	.	1	.	9	.	6	.	.	52
NG03/NG03E-Early Death *	.	.	38	11	1	5	6	1	.	.	2	7	3	.	11	4	.	89
NG03E-Early Death **	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
NG03E-Early Death ***	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	1
NG05-Late Clinical Outcome	.	.	.	1	.	1	.	.	.	.	.	.	1	.	.	.	.	3
NG07-Respiratory Support	.	.	2	2	1	.	1	.	.	1	1	7	.	.	.	1	1	17
NG08-Infant Status & Culture	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1	1
	4	**4**	**45**	**22**	**5**	**40**	**15**	**8**	**.**	**1**	**5**	**16**	**25**	**2**	**17**	**6**	**2**	**217**

** NG03 or NG03E are missing but infant is at least 120 days + 1 month past birthdate.*
*** NG03E is missing and NG03 is keyed but infant died <= 12 hours (per NG02).*
**** NG03E is keyed but infant did not die <= 12 hours (per NG02).*
***** NG05 is keyed by there is not NG03 form.*
+ NG08A is keyed but Question A2 on NG08 is not YES.
++ NG08C is keyed but Question A1 on NG08 is not YES.
+++ NG08LB_A is keyed but Question A4 on NG08 is not YES.
++++ NG08LB_B is keyed but Question A5 on NG08 is not YES.
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.4

Summary of Missing Hypothermia Follow-up Forms
By Form Type and Center

	Clinical Center																	
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
HF08 - Adapted Ver. Impact On Family	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1
HF09 - Bayley Scales Summary Score	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1
HF10 - Hearing Assessment	.	.	.	.	3	.	.	.	.	.	.	.	.	.	.	.	.	3
HF11 - Vision Assessment	.	.	.	.	3	.	.	.	.	.	.	.	.	.	.	.	.	3
HF13 - Summary of 19 Month Visit	.	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1
	.	.	.	.	**6**	.	.	.	.	.	.	**3**	.	.	.	.	.	**9**

Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.8

Summary of Missing Benchmarking Intervention Forms
By Form Type and Center

	Clinical Center																
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
BP08REDU-Reduction Phase	.	.	.	.	.	.	.	.	.	.	1	.	.	.	.	.	1
	.	.	.	.	.	.	.	.	.	.	**1**	.	.	.	.	.	**1**

+ Benchmarking is a GDB Subset. A matching GDB NG01 is expected.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.12

Summary of Missing Phototherapy Forms
By Form Type and Center

	Clinical Center																
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
BAER01	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
PHT03 - Laboratory Level	.	.	2	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2
PHT05 - Exchange Transfusions	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
PHT06 - Protocol Deviation	.	.	4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	4
PHT10 - Hearing Assessment	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
	.	.	**9**	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**9**

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.13

Summary of Missing aEEG Forms
By Form Type and Center

	Clinical Center															
Form Type	CW	TX Dal.	TX Hstn.	WS	MI	EM	CN	IN	YL	BR	ST	AL	DU	WF	NY	UCSD	Total
AE02 - Eligibility	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
AE03 - Maternal Baseline	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
AE04 - Neonatal Information	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
AE06 - Data During 72 Hrs	.	.	.	5	.	.	.	.	.	.	.	.	.	.	.	.	5
AE08 - Imaging Studies	.	.	.	3	.	.	.	.	.	.	.	.	.	.	.	.	3
AE09 - Status Form	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
AE10 - Discharge Diagnosis	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	1
AE12 - Buccal Smear Coll.	.	.	.	1	1	1	.	.	.	1	.	.	.	.	.	.	4
	.	.	.	**14**	**1**	**1**	.	.	.	**1**	.	.	.	.	.	.	**17**

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.14A

Number of Required Follow-up Forms Missing Among Those Completing 18 Month Visits or Lost-to-Follow-up
Whether or not the Form was Indicated as Completed on the NF11
Follow-up Window End Date between 01/01/98 and 06/30/06
By Form Type and Center

	Clinical Center																	
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
NF01-SES At Discharge	.	15	85	15	4	50	64	14	.	2	.	91	.	.	1	1	1	343
NF03-SES At 18 + 4 Months	1	1	5	.	3	.	1	2	.	5	.	.	.	.	2	.	9	29
NF04-Medical History	.	1	6	1	3	.	1	3	.	4	.	1	1	.	7	1	12	41
NF04A-Rehospitalization	2	1	2	6	.	.	1	.	.	1	.	2	.	.	.	.	2	17
NF05-Child Examination	.	1	4	11	12	1	.	.	.	.	.	.	.	.	.	1	28	58
NF06-Functional Status II	7	1	9	4	7	1	3	8	2	14	2	7	1	.	.	1	8	75
NF07-Family Resource Scale	12	2	14	11	7	1	4	17	17	18	3	11	2	.	1	1	15	136
NF08-Impact on the Family-G	6	1	7	4	6	1	4	5	1	11	2	6	1	.	.	1	6	62
NF09-Bayley Scales Summary	2	1	5	12	17	.	39	1	.	6	.	22	1	.	.	1	32	139
NF11-Summary 18 Mon. Visit	2	.	4	3	1	1	.	.	.	1	2	5	1	.	.	1	2	23
NF12-Lost-To-Follow-up	.	1	1	15	4	1	1	.	.	6	.	4	1	.	.	1	27	62
NF13-BITSEA	3	1	111	9	5	.	2	7	12	11	2	8	1	.	6	2	38	218
	35	**26**	**253**	**91**	**69**	**56**	**120**	**57**	**32**	**79**	**11**	**157**	**9**		**17**	**11**	**180**	**1203**

(All Follow-ups Completed between 01/01/98 and 06/30/06 according to the NF10 - Table Produced on 07/11/06)
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.14B

Number of Required Follow-up Forms Missing Among Those Completing 18 Month Visits and Indicating the Form was Completed on the NF11 Follow-up Window End Date between 01/01/98 and 06/30/06 By Form Type and Center

	Clinical Center																	
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
NF01-SES At Discharge	.	.	1	.	.	.	.	.	.	.	.	6	.	.	.	1	.	8
NF03-SES At 18 + 4 Months	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1
NF04-Medical History	.	.	1	.	.	.	.	.	.	.	.	.	1	.	.	.	.	2
NF04A-Rehospitalization	1	1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	4
NF05-Child Examination	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	.	2	3
NF07-Family Resource Scale	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	2
NF09-Bayley Scales Summary	.	.	.	.	3	.	.	.	.	.	.	.	.	.	.	1	1	5
NF13-BITSEA	1	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	2
	3		**3**		**4**							**6**	**1**			**2**	**7**	**25**

(All Follow-ups Completed between 01/01/98 and 06/30/06 according to the NF10 - Table Produced on 07/11/06)
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.15A

GDB Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2005 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on NF10***	Follow-up completed based on forms	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	NF10 FU rate*	Official FU rate**
3:Case Western Univ.	72	66	65	0	2	1	5	91.67%	90.28%
4:Univ. of Texas (D)	56	51	51	1	0	3	2	91.07%	91.07%
5:Wayne State Univ.	64	55	51	1	8	6	2	85.94%	79.69%
8:Univ. of Miami	155	141	141	1	3	5	9	90.97%	90.97%
9:Emory University	93	73	67	2	2	8	12	78.49%	72.04%
11:Univ. of Cincinnati	156	143	138	2	5	5	8	91.67%	88.46%
12:Indiana Univ.	142	127	125	2	4	2	13	89.44%	88.03%
13:Yale University	80	70	69	0	1	5	5	87.50%	86.25%
14:Brown University	129	120	120	1	1	1	8	93.02%	93.02%
15:Stanford University	67	62	62	0	0	4	1	92.54%	92.54%
16:Univ. of Alabama	152	133	132	3	2	2	18	87.50%	86.84%
18:Univ. of Texas (H)	152	128	127	2	6	24	0	84.21%	83.55%
19:Duke University	79	64	63	1	3	10	5	81.01%	79.75%
20:Wake Forest	136	125	125	1	2	7	4	91.91%	91.91%
21:Children's (NY)	55	49	49	0	2	0	6	89.09%	89.09%
22:Univ. of Calif. at San Diego	127	99	98	3	1	2	26	77.95%	77.17%
	1715	**1506**	**1483**	**20**	**42**	**85**	**124**	**87.81%**	**86.47%**

** FU visit made according to the NF10.*
*** FU visit made according to receipt of certain forms.*
**** FU completed based NF10 contains FU completed at another center.*
(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NF10.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.15B

GDB Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2004 and 12/31/2004

Center	Follow-up expected	Follow-up completed based on NF10***	Follow-up completed based on forms	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	NF10 FU rate*	Official FU rate**
3:Case Western Univ.	63	60	60	0	0	0	3	95.24%	95.24%
4:Univ. of Texas (D)	49	47	47	1	0	0	2	95.92%	95.92%
5:Wayne State Univ.	51	45	45	2	3	0	6	88.24%	88.24%
8:Univ. of Miami	80	72	72	1	1	0	7	90.00%	90.00%
9:Emory University	62	61	61	0	3	0	1	98.39%	98.39%
11:Univ. of Cincinnati	113	106	106	0	2	0	7	93.81%	93.81%
12:Indiana Univ.	94	81	81	1	1	0	13	86.17%	86.17%
13:Yale University	57	48	48	4	0	0	9	84.21%	84.21%
14:Brown University	87	77	77	0	2	0	10	88.51%	88.51%
15:Stanford University	44	42	42	0	0	0	2	95.45%	95.45%
16:Univ. of Alabama	107	100	100	2	1	0	7	93.46%	93.46%
18:Univ. of Texas (H)	102	91	90	0	5	0	11	89.22%	88.24%
19:Duke University	63	54	54	0	1	1	8	85.71%	85.71%
20:Wake Forest	88	86	86	1	0	0	2	97.73%	97.73%
21:Children's (NY)	59	47	46	0	1	0	12	79.66%	77.97%
22:Univ. of Calif. at San Diego	94	73	72	0	0	0	21	77.66%	76.60%
	1213	**1090**	**1087**	**12**	**20**	**1**	**121**	**89.86%**	**89.61%**

* *FU visit made according to the NF10.*
** *FU visit made according to receipt of certain forms.*
*** *FU completed based NF10 contains FU completed at another center.*
(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NF10.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.16A

Non-Missing Data for Key Variables at the 18-22 Month Follow-up for Those Completing the Visit According to the NF10 Follow-up Window End Date between 01/01/2006 and 06/30/2006

		GMF		_MDI_		_PDI_		_CP_		_Vision_		_Hearing_		_Weight_		_Length_		_Head_		_NDI_	
	N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
3: CW	66	66	100	66	100	61	92.4	66	100	66	100	62	93.9	66	100	65	98.5	66	100	65	98.5
4: TX Dal.	51	51	100	51	100	51	100	51	100	51	100	43	84.3	51	100	51	100	51	100	51	100
5: WS	55	52	94.5	52	94.5	51	92.7	52	94.5	52	94.5	44	80.0	51	92.7	51	92.7	51	92.7	50	90.9
8: MI	141	141	100	140	99.3	141	100	141	100	141	100	135	95.7	141	100	141	100	140	99.3	140	99.3
9: EM	73	71	97.3	65	89.0	61	83.6	70	95.9	71	97.3	58	79.5	72	98.6	71	97.3	72	98.6	60	82.2
11: CN	143	143	100	126	88.1	126	88.1	143	100	143	100	137	95.8	143	100	143	100	142	99.3	126	88.1
12: IN	127	125	98.4	107	84.3	106	83.5	125	98.4	126	99.2	115	90.6	127	100	127	100	127	100	107	84.3
13: YL	70	70	100	65	92.9	66	94.3	70	100	70	100	61	87.1	70	100	70	100	70	100	65	92.9
14: BR	120	120	100	113	94.2	116	96.7	120	100	120	100	106	88.3	120	100	120	100	120	100	116	96.7
15: ST	62	62	100	61	98.4	61	98.4	62	100	62	100	60	96.8	62	100	62	100	62	100	62	100
16: AL	133	133	100	129	97.0	129	97.0	133	100	133	100	117	88.0	133	100	133	100	133	100	129	97.0
18: TX Hstn.	128	128	100	122	95.3	122	95.3	128	100	128	100	121	94.5	127	99.2	128	100	128	100	125	97.7
19: DU	64	64	100	61	95.3	61	95.3	64	100	64	100	49	76.6	64	100	64	100	64	100	61	95.3
20: WF	125	125	100	125	100	125	100	125	100	125	100	115	92.0	125	100	125	100	125	100	125	100
21: NY	49	49	100	48	98.0	47	95.9	49	100	49	100	46	93.9	49	100	49	100	49	100	48	98.0
22: UCSD	99	99	100	96	97.0	97	98.0	99	100	98	99.0	90	90.9	99	100	99	100	99	100	92	92.9
	1506	**1499**	**99.5**	**1427**	**94.8**	**1421**	**94.4**	**1498**	**99.5**	**1499**	**99.5**	**1359**	**90.2**	**1500**	**99.6**	**1499**	**99.5**	**1499**	**99.5**	**1422**	**94.4**

NDI - MDI < 70 or PDI < 70 or Moderate/Severe CP or Blind in both eyes or Hearing aids in both ears. If any of these is true or if all are non-missing and untrue, then the NDI variable is non-missing. Otherwise it is missing
(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.16B

Non-Missing Data for Key Variables at the 18-22 Month Follow-up for Those Completing the Visit According to the NF10 Follow-up Window End Date between 01/01/2005 and 12/31/2005

		GMF		_MDI_		_PDI_		_CP_		_Vision_		_Hearing_		_Weight_		_Length_		_Head_		_NDI_	
	N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
3: CW	60	60	100	59	98.3	59	98.3	60	100	60	100	60	100	60	100	60	100	60	100	58	96.7
4: TX Dal.	47	47	100	47	100	47	100	47	100	47	100	47	100	47	100	47	100	47	100	47	100
5: WS	45	45	100	43	95.6	43	95.6	45	100	45	100	45	100	45	100	45	100	45	100	44	97.8
8: MI	72	72	100	72	100	72	100	72	100	72	100	70	97.2	72	100	72	100	72	100	72	100
9: EM	61	61	100	46	75.4	45	73.8	61	100	61	100	60	98.4	61	100	61	100	61	100	44	72.1
11: CN	106	106	100	96	90.6	96	90.6	106	100	106	100	106	100	106	100	106	100	106	100	96	90.6
12: IN	81	81	100	71	87.7	71	87.7	81	100	81	100	80	98.8	81	100	81	100	81	100	75	92.6
13: YL	48	48	100	46	95.8	46	95.8	47	97.9	48	100	48	100	48	100	48	100	48	100	46	95.8
14: BR	77	77	100	74	96.1	74	96.1	77	100	77	100	77	100	77	100	77	100	77	100	75	97.4
15: ST	42	42	100	37	88.1	37	88.1	42	100	42	100	42	100	42	100	42	100	42	100	37	88.1
16: AL	100	100	100	94	94.0	93	93.0	100	100	100	100	99	99.0	100	100	100	100	99	99.0	95	95.0
18: TX Hstn.	91	90	98.9	80	87.9	79	86.8	90	98.9	90	98.9	90	98.9	90	98.9	90	98.9	90	98.9	81	89.0
19: DU	54	54	100	50	92.6	51	94.4	54	100	54	100	54	100	54	100	54	100	54	100	51	94.4
20: WF	86	86	100	84	97.7	86	100	86	100	86	100	86	100	86	100	86	100	86	100	85	98.8
21: NY	47	47	100	44	93.6	36	76.6	47	100	46	97.9	46	97.9	47	100	47	100	47	100	41	87.2
22: UCSD	73	73	100	70	95.9	69	94.5	73	100	71	97.3	72	98.6	73	100	72	98.6	73	100	69	94.5
	1090	**1089**	**99.9**	**1013**	**92.9**	**1004**	**92.1**	**1088**	**99.8**	**1086**	**99.6**	**1082**	**99.3**	**1089**	**99.9**	**1088**	**99.8**	**1088**	**99.8**	**1016**	**93.2**

NDI - MDI < 70 or PDI < 70 or Moderate/Severe CP or Blind in both eyes or Hearing aids in both ears. If any of these is true or if all are non-missing and untrue, then the NDI variable is non-missing. Otherwise it is missing
(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.17

18-22 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
03	Case Western University				***Harriet Friedman (Bayley)***
		Dee Wilson	9/16/2005	---	
		Bonnie Siner	11/22/2002	---	
04	University of Texas at Dallas	Roy Heyne	9/16/2005	---	
		Cathy Boatman	---	8/2/2005	
05	Wayne State Univ.	Yvette Johnson	9/4/2004	---	
		Seetha Shankaran	9/16/2005	---	
		Laura Goldston	---	7/1/2005	
		Rebecca Wheeler	---	10/31/2005	
08	Univ. of Miami				***Silvia Frade (Bayley)***
		Charles Bauer	9/16/2005	---	
		Sylvia Hiriart	12/16/2004	---	
		Ann Londono	12/16/2004	---	
		Alexis Diaz	---	8/19/2005	
		Alexis Diaz	---	8/19/2005	
		Maria Calejo	---	8/19/2005	
		Yamiley Gideon	---	7/1/2004	
		Yamiley Gideon	---	7/1/2004	
		Alexis Diaz	---	8/19/2005	
		Maria Calejo	---	8/19/2005	
		Alexandra Stoerger	---	12/2/2005	
09	Emory University	Barbara Stoll	1/28/2004	---	
		Ira Adams-Chapman	9/16/2005	---	
		Judson Miller	5/17/2004	---	
		Gloria Smikle	5/17/2004	---	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.17

18-22 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
		Elisabeth Dinkins	5/17/2004	---	
		Linda Black	5/17/2004	---	
		Sheena Carter	---	11/8/2005	
11	University of Cincinnati	Jean Steichen	9/16/2005	---	
		Tari Gratton	9/16/2005	---	***Tari Gratton (Bayley)***
12	Indiana University	Anna Dusick	9/16/2005	---	
		Marilyn Bull	1/9/2006	---	
		Carolyn Lytle	1/9/2006	---	
		Darlene Kardatzke	1/9/2006	---	
		Greg Eaken	---	9/11/2004	
		Ann Cook	---	8/22/2005	
		Heike Minnich	---	5/25/2005	
13	Yale University	Linda Mayes	11/22/2002	---	
		Elaine Romano	9/16/2005	---	
		Richard Ehrenkranz	9/16/2005	---	
14	Brown Univ.				***Terri Leach (Bayley)***
					Betty Vohr (Neuro)
		Regina Gargus	2/9/2005	---	
		Barbara Alksininis	3/1/2005	---	
		Bill Cashore	2/9/2005 (4/14/2003)	---	
		Kalida Mehta	3/25/2003	---	
		Shabnam Lainwala	2/9/2005	---	
		Bonnie Stephens	2/9/2005	---	
		James Moore	2/9/2005	---	
		Vicky Watson	---	4/28/2004	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.17

18-22 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
		Martha Leonard	---	5/12/2004	
15	Stanford University	Susan Hintz	12/16/2004	---	
		Barry Fleisher	1/26/2005	---	
		Jean Kohn	1/26/2005	---	
		Monica Hajdena-Dawson	1/26/2005	---	
		Anne M DeBattista	1/26/2005	---	
		Dharshi Sivakumar	1/26/2005	---	
		Julie Lee	---	4/3/2003	
		Joan M Baran	---	3/23/2005	
		Nicholas St John	---	4/1/2003	
		Ginger Brudos	---	11/25/2005	
16	University of Alabama	Kathleen Nelson	11/22/2002	---	
		Myriam Peralta	9/16/2005	---	
		Julie Preskitt	5/1/2003	---	
		Sally Whitley	10/14/2005	---	
		Mary Beth Moses	10/14/2005	---	
		Fred Biasini	---	11/8/2005	
		Kirstin Bailey	---	7/13/2004	
		Stephanie Chopko	---	5/1/2003	
		Richard Rector	---	4/2/2004	
18	University of Texas at Houston	Brenda Morris	12/16/2004	---	
		Pam Bradt	1/28/2004	---	
		Terri Major-Kincade	4/24/2003	---	
		Laura Whitely	12/16/2004	---	
		Jon Tyson	9/16/2005	---	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.17

18-22 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
		Susan Dieterich	---	7/7/2003	
19	Duke University	Ricki Goldstein	9/28/2004	---	
		William Malcolm	---	5/20/2004	
		Kathryn Gustafson	---	1/17/2006	
20	Wake Forest University	Robert Dillard	12/16/2004	---	
		Lisa Washburn	1/10/2005	---	
		Michael O'Shea	9/16/2005	---	
		Cherie Heller	1/10/2005	---	
		Barbara Jackson	1/10/2005	1/14/2003	
		Don Goldstein	---	7/1/2002	
		Gail Hounshell	---	8/10/2005	
		Carol Peterson	---	11/26/2002	
		Melissa Morris	---	9/13/2005	
		Raquel Halfond	---	7/5/2005	
		Korinne Chiu	---	11/29/2005	
		Debbie Allred	---	8/9/2005	
		Ellen Waldrep	---	9/27/2005	
21	University of Rochester	Gary Myers	9/28/2004	---	
		Jonathan Mink	6/26/2003	---	
		Carlos Torres	6/26/2003	---	
		Harris Gelbard	6/26/2003	---	
		David Wang	6/26/2003	---	
		Lauren Zwetsch	9/16/2005	---	
		Lisa Augostino	6/26/2003	---	
		Kelly Yost	---	8/2/2005	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.17

18-22 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
22	University of California at San Diego	Yvonne Vaucher	9/16/2005	---	
		Paul Zlotnik	1/1/2003	---	
		Cheryl Runyan	8/27/2003	---	
		Martha Fuller	9/16/2005	8/4/2004	
		Meghan Lukasik	---	3/1/2003	
		James Wilkes	---	3/1/2003	
		Elaine Ito	---	3/1/2003	
		Rene Barbieri-Welge	---	3/1/2003	
		Ayala Ben-Tall	---	3/1/2003	
		Deborah Pontillo	---	3/1/2003	
		Donna Posin	---	10/6/2005	
91	University of Wisconsin	Laurel Bear	12/16/2004	---	
		Christine Casey	---	3/1/2003	
		Paula Jackson	---	3/1/2003	
92	Northwestern University	Marissa De'Ungria	1/28/2004	---	
		Marie Weissbourd	---	1/12/2005	
93	University of Florida	David Childers	9/28/2004	12/22/2004	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.18A

Hypothermia Pilot Study Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2001 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on HF12	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	HF12 FU rate
3:Case Western Univ.	1	1	0	0	0	0	100.0%
4:Univ. of Texas (D)	2	2	0	1	0	0	100.0%
5:Wayne State Univ.	.	.	.	.	.	.	.
8:Univ. of Miami	.	.	.	.	.	.	.
9:Emory University	.	0	0	1	0	0	.
11:Univ. of Cincinnati	1	1	0	0	0	0	100.0%
12:Indiana Univ.	2	2	0	0	0	0	100.0%
13:Yale University	1	0	0	0	0	1	0.00%
14:Brown University	2	2	0	0	0	0	100.0%
15:Stanford University	.	.	.	.	.	.	.
16:Univ. of Alabama	1	1	0	0	0	0	100.0%
18:Univ. of Texas (H)	2	2	0	0	0	0	100.0%
19:Duke University	.	.	.	.	.	.	.
20:Wake Forest	.	.	.	.	.	.	.
21:Children's (NY)	.	.	.	.	.	.	.
22:Univ. of Calif. at San Diego	.	.	.	.	.	.	.
	12	**11**	**0**	**2**	**0**	**1**	**91.67%**

(All Follow-ups Completed Between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the HF12.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.18B

Hypothermia Main Study Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2001 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on HF12	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	HF12 FU rate
3:Case Western Univ.	5	5	0	2	0	0	100.0%
4:Univ. of Texas (D)	13	13	0	2	0	0	100.0%
5:Wayne State Univ.	28	27	1	2	0	0	100.0%
8:Univ. of Miami	8	8	0	0	0	0	100.0%
9:Emory University	5	5	0	1	0	0	100.0%
11:Univ. of Cincinnati	8	8	0	0	0	0	100.0%
12:Indiana Univ.	5	5	0	2	0	0	100.0%
13:Yale University	8	7	0	1	0	1	87.50%
14:Brown University	5	4	0	0	0	1	80.00%
15:Stanford University	4	4	0	2	0	0	100.0%
16:Univ. of Alabama	20	20	0	0	0	0	100.0%
18:Univ. of Texas (H)	17	17	0	1	0	0	100.0%
19:Duke University	5	5	0	0	0	0	100.0%
20:Wake Forest	.	.	.	.	.	.	.
21:Children's (NY)	1	1	0	0	0	0	100.0%
22:Univ. of Calif. at San Diego	14	11	0	1	0	3	78.57%
	146	**140**	**1**	**14**	**0**	**5**	**96.58%**

(All Follow-ups Completed Between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the HF12.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.19

Glutamine 30 Months Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2002 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on NFT10	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	NFT10 FU rate
3:Case Western Univ.	63	53	0	0	0	10	84.13%
4:Univ. of Texas (D)	68	62	0	0	0	7	91.18%
5:Wayne State Univ.	49	43	2	1	0	4	91.84%
8:Univ. of Miami	95	79	0	0	0	16	83.16%
9:Emory University	80	68	0	0	0	12	85.00%
11:Univ. of Cincinnati	116	103	0	0	0	14	88.79%
12:Indiana Univ.	103	75	2	4	0	26	74.76%
13:Yale University	62	46	0	0	0	16	74.19%
14:Brown University	97	82	0	0	0	15	84.54%
15:Stanford University	37	33	0	0	0	4	89.19%
16:Univ. of Alabama	134	111	2	0	0	23	84.33%
22:Univ. of Calif. at San Diego	18	13	1	0	0	4	77.78%
	922	**768**	**7**	**5**	**0**	**151**	**84.06%**

(All Follow-ups Completed between 01/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NFT10.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.20

Number of Required Follow-up Forms Missing Among Those Completing 30 Month Visits and Indicating the Form was Completed on the NFT11 Follow-up Window End Date between 01/01/02 and 06/30/06 By Form Type and Center

	Clinical Center												
Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	UCSD	Total
NFT12-Lost-To-Follow-up	1	.	.	.	.	.	.	.	.	.	.	.	.	1
NFT14-PPVT	4	.	.	.	.	.	.	.	.	.	.	.	.	4
	5													**5**

(All Follow-ups Completed between 01/01/98 and 06/30/06 according to the NF10 - Table Produced on 07/11/06)
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.21

28-32 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
03	Case Western University				***Harriet Friedman (Bayley)***
		Dee Wilson	9/28/2004	---	
04	University of Texas at Dallas	Roy Heyne	9/28/2004	---	
		Cathy Boatman	---	7/24/2003	
05	Wayne State Univ.	Yvette Johnson	9/4/2004	---	
		Laura Goldston	---	6/28/2004	
08	Univ. of Miami				***Silvia Frade (Bayley)***
		Charles Bauer	9/28/2004	---	
		Alexis Diaz	---	3/1/2004	
		Alexis Diaz	---	3/1/2004	
		Maria Calejo	---	3/1/2004	
		Yamiley Gideon	---	3/1/2004	
		Yamiley Gideon	---	3/1/2004	
		Alexis Diaz	---	3/1/2004	
		Maria Calejo	---	3/1/2004	
09	Emory University	Barbara Stoll	1/28/2004	---	
		Ira Adams-Chapman	9/28/2004	---	
		Sheena Carter	---	3/1/2003	
11	University of Cincinnati	Jean Steichen	9/28/2004	---	
		Tari Gratton	9/28/2004	---	***Tari Gratton (Bayley)***
12	Indiana University	Anna Dusick	9/28/2004	---	
		Greg Eaken	---	6/26/2003	
13	Yale University	Elaine Romano	9/28/2004	---	
		Nancy Close	---	2/9/2005	
14	Brown Univ.				***Terri Leach (Bayley)***

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 1.21

28-32 Month Follow-up Certification Report
By Center

ID	Site Name	Examiner	Neurological Exam Date Certified:	Bayley Date Certified:	Study-Level Certifier Neuro or Bayley
					Betty Vohr (Neuro)
		Vicky Watson	---	4/28/2004	
		Martha Leonard	---	5/12/2004	
15	Stanford University	Susan Hintz	12/16/2004	---	
		Barry Fleisher	1/26/2005	---	
		Jean Kohn	1/26/2005	---	
		Monica Hajdena-Dawson	1/26/2005	---	
		Anne M DeBattista	1/26/2005	---	
		Dharshi Sivakumar	1/26/2005	---	
		Julie Lee	---	3/1/2003	
		Joan M Baran	---	4/1/2003	
		Nicholas St John	---	4/1/2003	
16	University of Alabama	Myriam Peralta	9/28/2004	---	
		Mary Beth Moses	10/16/2003	---	
		Stephanie Chopko	---	5/1/2003	
		Richard Rector	---	4/2/2004	
18	University of Texas at Houston	Pam Bradt	1/28/2004	---	
19	Duke University	Ricki Goldstein	---	9/16/2005	
		William Malcolm	---	5/22/2004	
21	University of Rochester	Gary Myers	9/28/2004	---	
22	University of California at San Diego	Yvonne Vaucher	9/28/2004	---	
		Martha Fuller	1/28/2004	---	

Any pending certification dates are shown in parentheses underneath the certified date.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.22

Preemie INO Main Study Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2003 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on PNF10/NF10	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	PNF10/NF10 FU rate
4:Univ. of Texas (D)	19	18	0	1	0	1	94.74%
5:Wayne State Univ.	9	8	1	0	0	0	100.0%
9:Emory University	6	6	0	0	0	0	100.0%
11:Univ. of Cincinnati	9	9	0	0	0	0	100.0%
12:Indiana Univ.	17	14	1	2	0	2	88.24%
13:Yale University	7	7	0	0	0	0	100.0%
14:Brown University	25	24	0	0	0	1	96.00%
15:Stanford University	7	7	0	1	0	0	100.0%
16:Univ. of Alabama	19	17	1	0	0	1	94.74%
18:Univ. of Texas (H)	17	17	0	1	0	0	100.0%
20:Wake Forest	15	15	0	0	0	0	100.0%
21:Children's (NY)	5	5	0	0	0	0	100.0%
22:Univ. of Calif. at San Diego	13	11	0	0	0	2	84.62%
91:Univ. of Wisconsin	6	5	0	0	0	1	83.33%
92:Northwestern Univ.	16	3	0	0	13	0	18.75%
93:Univ. of Florida	23	19	0	0	0	4	82.61%
	213	**185**	**3**	**5**	**13**	**12**	**88.26%**

(All Follow-ups Completed Between 01/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PNF10.
This table includes all Preemie INO infants from the Main study (birth weight <= 1500).

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.23

Phototherapy Study Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2004 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on NF10	Follow-up completed based on forms	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	NF10 FU rate	Official FU rate
3:Case Western Univ.	43	42	42	0	1	0	1	97.67%	97.67%
4:Univ. of Texas (D)	50	46	46	0	0	2	2	92.00%	92.00%
5:Wayne State Univ.	23	19	19	1	6	3	0	86.96%	82.61%
8:Univ. of Miami	102	97	97	1	3	2	3	96.08%	95.10%
9:Emory University	38	33	32	0	3	1	4	86.84%	84.21%
11:Univ. of Cincinnati	60	54	49	1	1	2	4	91.67%	81.67%
12:Indiana Univ.	79	76	76	1	3	1	2	97.47%	96.20%
13:Yale University	39	35	34	0	1	4	0	89.74%	87.18%
14:Brown University	72	67	67	0	1	0	5	93.06%	93.06%
15:Stanford University	34	31	31	0	0	3	0	91.18%	91.18%
16:Univ. of Alabama	116	103	103	1	1	1	12	89.66%	88.79%
18:Univ. of Texas (H)	95	80	78	2	4	14	1	86.32%	82.11%
19:Duke University	38	28	28	0	2	5	5	73.68%	73.68%
20:Wake Forest	57	53	53	1	2	2	2	94.74%	92.98%
21:Children's (NY)	35	34	34	0	1	0	1	97.14%	97.14%
22:Univ. of Calif. at San Diego	49	42	42	1	0	1	6	87.76%	85.71%
	930	**840**	**831**	**9**	**29**	**41**	**48**	**91.29%**	**89.35%**

(All Follow-ups Completed Between 01/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NF10.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.24

Non-Missing Data for Key Variables at the 18-22 Month Follow-up for Those Completing the Visit According to the NF10 Phototherapy Follow-up Window End Date between 01/01/2004 and 06/30/2006

		GMF		_MDI_		_PDI_		_CP_		_Vision_		_Hearing_		_Weight_		_Length_		_Head_		_NDI_	
	N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
3: CW	42	42	100	42	100	39	92.9	42	100	42	100	38	90.5	42	100	42	100	42	100	42	100
4: TX Dal.	46	46	100	46	100	46	100	46	100	46	100	39	84.8	46	100	46	100	46	100	46	100
5: WS	19	19	100	19	100	18	94.7	19	100	19	100	13	68.4	19	100	19	100	19	100	18	94.7
8: MI	97	97	100	97	100	97	100	97	100	97	100	91	93.8	97	100	97	100	96	99.0	97	100
9: EM	33	32	97.0	31	93.9	30	90.9	33	100	33	100	29	87.9	33	100	33	100	33	100	30	90.9
11: CN	54	54	100	47	87.0	47	87.0	54	100	54	100	49	90.7	54	100	54	100	54	100	47	87.0
12: IN	76	76	100	65	85.5	64	84.2	76	100	76	100	71	93.4	76	100	76	100	76	100	64	84.2
13: YL	35	35	100	33	94.3	33	94.3	35	100	35	100	34	97.1	35	100	35	100	35	100	33	94.3
14: BR	67	67	100	66	98.5	66	98.5	67	100	67	100	57	85.1	67	100	67	100	67	100	66	98.5
15: ST	31	31	100	31	100	31	100	31	100	31	100	30	96.8	31	100	31	100	31	100	31	100
16: AL	103	103	100	100	97.1	100	97.1	103	100	103	100	90	87.4	103	100	103	100	103	100	100	97.1
18: TX Hstn.	80	79	98.8	74	92.5	74	92.5	79	98.8	79	98.8	75	93.8	78	97.5	79	98.8	79	98.8	76	95.0
19: DU	28	28	100	28	100	28	100	28	100	28	100	23	82.1	28	100	28	100	28	100	28	100
20: WF	53	53	100	53	100	53	100	53	100	53	100	50	94.3	53	100	53	100	53	100	53	100
21: NY	34	34	100	34	100	32	94.1	34	100	34	100	33	97.1	34	100	34	100	34	100	34	100
22: UCSD	42	42	100	41	97.6	42	100	42	100	42	100	39	92.9	42	100	42	100	42	100	40	95.2
	840	**838**	**99.8**	**807**	**96.1**	**800**	**95.2**	**839**	**99.9**	**839**	**99.9**	**761**	**90.6**	**838**	**99.8**	**839**	**99.9**	**838**	**99.8**	**805**	**95.8**

NDI - MDI < 70 or PDI < 70 or Moderate/Severe CP or Blind in both eyes or Hearing aids in both ears. If any of these is true or if all are non-missing and untrue, then the NDI variable is non-missing. Otherwise it is missing

(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 1.25

aEEG Follow-Up Rate by Center for Infants with Follow-up Window End Date between 01/01/2001 and 06/30/2006

Center	Follow-up expected	Follow-up completed based on aEEGF12	Follow-up completed at another center	Died after discharge	Follow-up pending	Lost to follow-up	HF12 FU rate
3:Case Western Univ.	1	0	0	0		0	0%
4:Univ. of Texas (D)	2	2	0	0		0	100%
5:Wayne State Univ.	1	0	0	0		0	0%
8:Univ. of Miami	2	2	0	0		0	100%
9:Emory University	1	1	0	0		0	100%
11:Univ. of Cincinnati	0	0	0	0		0	%
12:Indiana Univ.	1	1	0	1		0	100%
13:Yale University	0	0	0	0		0	%
14:Brown University	1	0	0	1		0	0%
15:Stanford University	0	0	0	0		0	%
16:Univ. of Alabama	0	0	0	0		0	%
18:Univ. of Texas (H)	0	0	0	0		0	%
19:Duke University	0	0	0	0		0	%
20:Wake Forest	0	0	0	0		0	%
21:Children's (NY)	0	0	0	0		0	%
22:Univ. of Calif. at San Diego	0	0	0	0		0	%
	9	**6**	**0**	**2**			**66.67%**

(All Follow-ups Completed Between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the AF12.

CHAPTER TWO

Enrollment, Number of Follow-ups Completed, and Number of Forms Received

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.1A

Number of Infants Enrolled in the Generic Data Base
By Birth Month and Center

		Clinical Center																	
	Birth Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
RTI	Jun 2006	16	16	18	.	17	28	7	24	27	9	21	33	15	.	2	.	.	233
	May 2006	14	10	26	.	16	27	25	18	19	9	28	19	7	.	.	.	.	218
	Apr 2006	14	24	17	.	22	28	28	22	22	16	31	38	7	.	.	.	.	269
	Mar 2006	19	15	24	19	27	32	19	23	22	22	26	31	9	28	12	31	.	359
	Feb 2006	10	19	13	9	21	27	22	16	16	11	35	27	7	23	15	17	.	288
	Jan 2006	19	20	18	20	20	30	23	22	24	12	31	36	13	21	23	30	.	362
	Dec 2005	14	10	26	14	18	39	24	19	13	13	24	26	14	36	19	27	.	336
	Nov 2005	17	13	30	17	19	33	22	25	19	20	29	30	13	20	10	20	.	337
	Oct 2005	11	12	19	28	20	44	37	13	20	13	23	24	13	24	13	24	.	338
	Sep 2005	14	12	14	24	12	28	31	19	20	14	33	26	22	20	13	24	.	326
	Aug 2005	23	11	22	30	17	26	29	18	11	14	39	42	8	20	15	34	.	359
	Jul 2005	14	17	16	16	26	34	25	14	17	23	25	31	12	18	11	34	.	333
	Jun 2005	18	23	16	20	28	38	23	21	24	12	27	25	13	24	12	34	.	358
	May 2005	16	21	16	13	14	27	30	19	17	8	29	40	11	33	12	23	.	329
	Apr 2005	7	13	23	16	20	37	30	16	26	14	30	15	16	27	27	23	.	340
	Jan-Mar 2005	34	43	61	74	51	93	64	60	52	52	86	76	35	61	44	84	.	970
	2004	159	232	238	214	235	401	320	186	242	123	295	340	143	274	151	294	.	3847
	2003	157	162	241	289	201	380	297	162	250	138	302	344	139	280	151	290	.	3783
	2002	190	195	187	235	204	397	307	143	265	130	281	330	159	266	169	252	.	3710

(Infants in the Generic Data Base with Birth Dates on or before 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NG01.
Other sites include HV, TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.1A

Number of Infants Enrolled in the Generic Data Base
By Birth Month and Center

		Clinical Center																	
	Birth Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
	2001	190	203	213	256	230	387	311	152	259	126	304	320	159	312	159	278	44	3903
	2000	186	195	184	236	225	339	343	123	224	141	298	301	.	.	.	.	406	3201
	1999	185	193	223	217	212	365	395	158	219	190	277	234	.	.	.	.	791	3659
	1998	184	223	239	234	232	389	334	153	264	211	314	69	.	.	.	.	741	3587
		1511	**1682**	**1884**	**1981**	**1887**	**3229**	**2746**	**1426**	**2072**	**1321**	**2588**	**2457**	**815**	**1487**	**858**	**1519**	**1982**	**31445**
GW	1995-1997	620	733	672	699	698	872	830	426	586	520	359	.	.	.	.	.	1614	8629
	1993-1994	404	608	587	558	616	381	490	236	398	338	.	.	.	.	.	.	930	5546
	1991-1992	480	585	710	565	579	350	334	243	342	268	.	.	.	.	.	.	1017	5473
	1989-1990	451	629	879	657	.	.	.	.	.	.	.	.	.	.	.	.	758	3374
	1987-1988	289	349	466	383	.	.	.	.	.	.	.	.	.	.	.	.	441	1928
		2244	**2904**	**3314**	**2862**	**1893**	**1603**	**1654**	**905**	**1326**	**1126**	**359**	.	.	.	.	.	**4760**	**24950**
		3755	**4586**	**5198**	**4843**	**3780**	**4832**	**4400**	**2331**	**3398**	**2447**	**2947**	**2457**	**815**	**1487**	**858**	**1519**	**6742**	**56395**

(Infants in the Generic Data Base with Birth Dates on or before 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NG01.
Other sites include HV, TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.1B

Number of Infants Enrolled in the Generic Data Base
By Birth Month and Center
(Previous Years Only)

	Clinical Center																
Birth Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
Dec 2004	14	25	25	16	16	29	21	18	19	9	36	33	8	16	9	21	315
Nov 2004	14	16	18	15	16	43	29	25	23	8	17	23	12	22	9	14	304
Oct 2004	18	15	18	20	19	28	29	18	22	19	24	28	4	29	11	23	325
Sep 2004	9	21	23	22	20	24	20	4	14	10	28	38	15	21	11	40	320
Aug 2004	13	20	16	16	20	36	29	14	24	6	25	27	10	29	14	34	333
Jul 2004	15	17	17	13	19	33	25	15	22	11	27	17	10	16	10	20	287
Jun 2004	15	18	18	17	16	19	27	18	19	14	27	26	14	21	12	18	299
May 2004	21	20	18	19	19	43	26	20	27	10	18	33	16	30	17	24	361
Apr 2004	5	26	21	10	17	34	24	12	25	9	22	32	14	23	9	24	307
Mar 2004	11	15	21	21	24	31	33	11	22	7	32	33	7	16	17	30	331
Feb 2004	7	19	18	21	15	36	30	12	17	7	17	21	15	32	17	17	301
Jan 2004	17	20	25	24	34	45	27	19	8	13	22	29	18	19	15	29	364
	159	**232**	**238**	**214**	**235**	**401**	**320**	**186**	**242**	**123**	**295**	**340**	**143**	**274**	**151**	**294**	**3847**

(Infants in the Generic Data Base with Birth Dates on or before 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NG01.
Other sites include HV, TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.1C

Number of Forms in the Generic Data Base
By Form Type and Center

Form Type	CW	TX Dal.	WS	OTHER	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
NG01-Screening Log	1512	1682	1885	1983	1985	1887	3232	2747	1426	2072	1321	2591	2458	815	1491	858	1524	31469
NG02-Baseline	1509	1682	1878	1982	1982	1887	3205	2737	1418	2072	1321	2588	2457	800	1491	850	1524	31383
NG03-Clinical Outcome	1309	1416	1558	1826	1850	1727	2930	2461	1281	1877	1224	2430	2214	781	1369	779	1377	28409
NG03E-Early Death	157	238	209	156	107	129	234	223	110	146	72	92	158	14	117	41	114	2317
NG05-Late Clin. Outcome	116	104	75	80	336	151	187	174	105	97	92	200	230	67	73	52	66	2205
NG07-Respira. Support	1446	1620	1758	1969	1956	1842	3165	2654	1377	2007	1289	2506	2344	793	1481	820	1485	30512
NG08-Infant Status/Cul.	630	662	688	1488	969	744	1206	1182	476	783	519	991	936	171	312	159	280	12196
NG08A-Parenteral Thera.	3073	3104	2587	5783	4286	3811	4521	6323	2234	3002	2369	5095	4724	1050	1451	738	1250	55401
NG08C-Addition. Culture	2821	4372	2459	4537	3642	3834	3244	5482	2355	2494	2102	5696	4484	908	944	568	1107	51049
NG08CRP-C Reac. Protein	153	10	.	8296	2095	2905	.	7	.	.	2469	1	1	.	27	.	353	16317
NG08LB_A-Indwell. Line	1150	778	1351	2221	2549	1846	4057	1926	2631	1097	1363	1811	1532	578	860	473	829	27052
NG08LB_B-Blocker	116	240	155	174	429	383	282	887	471	257	371	166	292	85	137	49	78	4572
NG08M-Maternal Antibiotic	566	653	648	1397	741	678	1071	995	442	730	420	912	776	147	279	142	246	10843
	14558	**16561**	**15251**	**31892**	**22927**	**21824**	**27334**	**27798**	**14326**	**16634**	**14932**	**25079**	**22606**	**6209**	**10032**	**5529**	**10233**	**303725**

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.
Other sites include HV, TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 2.2A

Number of Infants Completing the 18 Month Follow-up Visit
By Month of Visit and Center

	Clinical Center																	
Final Visit Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
Jun 2006	1	6	.	1	6	3	8	1	5	.	3	7	2	7	3	.	.	53
May 2006	4	6	7	7	7	5	5	2	8	2	9	4	5	9	3	4	.	87
Apr 2006	5	4	4	2	3	7	7	4	5	2	10	11	4	6	6	7	.	87
Mar 2006	6	5	4	10	9	6	10	16	6	1	16	10	5	4	4	4	.	116
Feb 2006	4	8	5	9	3	12	9	3	5	2	6	8	3	9	2	4	.	92
Jan 2006	2	.	.	6	6	6	7	2	6	4	6	6	1	5	3	9	.	69
Dec 2005	2	.	3	5	1	2	7	6	5	2	5	5	2	6	5	7	.	63
Nov 2005	5	4	1	3	6	3	7	10	4	6	12	7	5	9	3	5	.	90
Oct 2005	2	6	.	6	8	5	3	5	7	5	10	7	3	5	5	4	.	81
Sep 2005	5	1	.	9	3	8	4	1	4	3	7	3	2	5	1	7	.	63
Aug 2005	2	5	3	9	3	8	9	6	12	2	6	9	3	6	3	6	.	92
Jul 2005	5	1	2	6	5	7	6	4	5	4	4	4	1	6	1	6	.	67
Jun 2005	4	3	1	11	5	13	9	4	7	2	10	4	4	12	3	6	.	98
May 2005	8	4	3	9	4	11	12	10	9	8	7	4	2	9	3	12	.	115
Apr 2005	7	1	5	15	5	16	10	1	6	4	8	10	7	4	3	7	.	109
Mar 2005	9	3	4	6	6	10	11	1	16	3	7	11	5	11	2	5	.	110
Feb 2005	1	4	5	7	3	8	7	5	5	3	7	12	6	10	2	3	.	88
Jan 2005	.	.	3	9	1	9	6	3	4	6	10	16	3	7	3	6	.	86
2004	62	48	51	89	54	97	76	38	82	41	98	83	43	74	41	72	.	1049

(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The final visit date is taken from the NF11.
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 2.2A

Number of Infants Completing the 18 Month Follow-up Visit
By Month of Visit and Center

	Clinical Center																	
Final Visit Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
2003	55	46	35	57	53	117	83	27	77	24	98	84	43	86	42	67	4	998
2002	64	39	52	72	69	100	70	31	76	38	92	107	.	10	6	1	86	913
2001	60	53	54	74	83	100	97	50	56	57	73	65	.	.	.	.	92	914
2000	55	40	68	94	47	93	80	31	75	58	90	20	.	.	.	.	83	834
1999	54	48	55	77	58	122	48	40	62	64	85	.	.	.	.	.	74	787
1998	64	51	60	74	51	80	54	34	51	47	37	.	.	.	.	.	85	688
Missing Date	2	.	4	3	1	1	.	.	.	1	2	5	1	.	.	2	2	24
	488	**386**	**429**	**670**	**500**	**849**	**645**	**335**	**598**	**389**	**718**	**502**	**150**	**300**	**144**	**244**	**426**	**7773**

(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The final visit date is taken from the NF11.
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 2.2B

Number of Follow-up Forms Completed
Between 01/01/98 and 06/30/06
By Form Type and Center

Form Type	CW	TX Dal.	WS	OTHER	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
NF00-Screening Log	512	416	464	521	747	575	938	834	430	664	443	793	560	175	316	177	313	8878
NF01-SES At Discharge	507	388	369	520	716	554	858	647	394	662	431	769	437	156	306	146	278	8138
NF03-SES At 18 + 4 Mon	490	396	426	421	687	500	853	651	341	602	385	726	502	152	301	141	257	7831
NF04-Medical History	491	396	425	416	677	500	853	656	340	602	386	726	501	151	301	135	255	7811
NF04A-Readmission	583	394	701	522	609	476	843	1057	476	787	243	881	618	126	298	112	225	8951
NF05-Child Examination	488	387	427	398	661	490	848	649	335	598	390	720	502	152	300	143	245	7733
NF07-Fami. Resource Scale	424	331	383	413	572	432	743	549	244	487	331	601	400	102	200	97	158	6467
NF08-Impact on Family-G	179	141	188	414	255	162	298	193	101	197	170	218	27	.	.	.	1	2544
NF09-Bayley Scales Summary	486	386	426	393	661	480	849	608	334	598	384	720	479	151	300	143	245	7643
NF10-Status	512	416	464	521	747	575	938	834	430	664	443	793	560	175	316	177	313	8878
NF11-Sum 18 Month Visit	498	399	428	434	684	502	848	692	406	658	418	727	514	151	301	144	290	8094
NF12-Lost-To-Follow-Up Ques	28	28	27	68	61	67	79	181	86	65	32	69	52	23	11	35	60	972
NF13-B1TSEA	211	173	48	.	311	224	404	324	154	289	130	386	340	151	300	135	245	3825
	5409	**4251**	**4776**	**5041**	**7388**	**5537**	**9352**	**7875**	**4071**	**6873**	**4186**	**8129**	**5492**	**1665**	**3250**	**1585**	**2885**	**87765**

(All Follow-ups Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period 01/01/98 to 06/30/06

Table 2.4B

Number of Forms in the Glutamine 30 Month Follow-up Study
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	UCSD	Total
NFT00-NFT00	53	62	43	78	68	99	74	46	82	33	110	13	761
NFT03-SES At Discharge	53	62	43	77	68	102	75	44	82	32	110	13	761
NFT04-Medical History	53	62	43	76	68	102	75	45	82	32	110	13	761
NFT04A-Readmission	12	8	6	13	15	16	53	24	35	6	21	3	212
NFT05-Child Examination	53	62	43	76	68	102	74	46	82	33	110	13	762
NFT07-Fami. Resource Scale	53	62	36	74	67	102	75	42	81	31	108	13	744
NFT09-Bayley Scales Summary	52	62	43	74	68	102	67	42	78	33	110	13	744
NFT10-Status	53	62	43	78	68	99	74	46	82	33	110	13	761
NFT11-Summary 30-Mo Visit	53	62	43	78	68	102	75	46	82	33	110	13	765
NFT12-Lost-To-Follow-Up Ques	20	6	1	16	1	13	27	16	15	.	23	4	142
NFT13-BITSEA	53	62	42	76	67	100	75	43	81	32	106	13	750
NFT14-PPVT	20	38	.	20	30	42	37	9	38	33	51	.	318
	528	**610**	**386**	**736**	**656**	**981**	**781**	**449**	**820**	**331**	**1079**	**124**	**7481**

(All Forms Completed between 01/01/02 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.5.1A

Number of Forms in the Hypothermia Secondary Study - Urinary Lactate/Creatinine Ratio
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	NY	UCSD	Total
IHU01-Urinary Lactate	8	11	26	9	6	6	4	5	5	3	6	11	6	3	11	120
IHU02-Sample Collection	8	11	26	9	6	6	4	5	5	3	6	8	5	1	11	114

(All Forms Completed between 05/01/01 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

The number of forms in IHU01 represents the number of infants enrolled.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.5.2A

Number of Forms in the Hypothermia Secondary Study - Cytokine
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	NY	UCSD	Total
HC03-Cytokines Sample	8	11	26	9	6	7	4	7	4	3	12	11	6	3	17	134
HC03S-Shipment Log	32	41	104	34	22	28	16	26	16	10	48	44	24	10	68	523

(All Forms Completed between 07/01/01 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

The number of forms in HC03 represents the number of infants enrolled.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.5.3A

Number of Forms in the Hypothermia Secondary Study - EEG
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	NY	UCSD	Total
HE01-A-EEG Infants	5	11	20	6	5	3	3	4	1	2	6	14	2	3	11	96
HE01S-Recordings Done	11	31	58	5	12	1	10	12	.	2	24	36	6	1	34	243

(All Forms Completed between 10/01/02 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

The number of forms in HE01S shows only those who answered 'Yes' to Question 1. Was Recording Done?

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.5.4A

Number of Forms in the Hypothermia Secondary Study - apoE
By Form Type and Center

Form Type	TX Dal.	WS	YL	BR	AL	NY	UCSD	Total
IHA01-Sample Collection	10	17	3	1	7	1	11	50

(All Forms Completed between 05/01/03 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.8A

Number of Infants Enrolled in the Benchmarking Intervention Study
By Birth Month and Center

	Clinical Center																
Birth Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
Aug 2004	.	.	.	.	.	.	.	3	.	.	.	.	.	.	.	.	3
Jul 2004	.	.	.	.	.	.	.	4	.	.	.	.	.	.	.	.	4
Jun 2004	.	.	.	.	.	.	.	7	.	.	.	.	.	.	.	.	7
May 2004	14	8	11	.	.	11	8	10	.	3	.	6	6	21	8	11	117
Apr 2004	2	13	9	.	4	4	7	7	.	4	.	11	9	16	5	11	102
Mar 2004	5	6	13	.	5	5	12	6	.	3	.	11	4	3	9	18	100
Feb 2004	4	12	8	.	3	5	6	8	.	3	.	9	8	15	10	6	97
Jan 2004	10	7	12	.	13	10	8	11	.	7	.	11	8	7	8	15	127
2003	94	77	98	.	55	76	63	94	.	60	.	143	86	167	96	148	1257
2002	99	110	95	.	47	76	84	86	.	64	.	122	81	130	96	137	1227
2001	96	107	101	44	47	76	59	65	38	46	42	99	71	123	72	109	1195
2000	.	.	.	28	.	.	.	.	29	.	53	.	.	.	.	.	110
	324	**340**	**347**	**72**	**174**	**263**	**247**	**301**	**67**	**190**	**95**	**412**	**273**	**482**	**304**	**455**	**4346**

(All Forms Completed between 10/01/00 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the BP00.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.8B

Number of Forms in the Benchmarking Intervention Study
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
BP00-Screening Wrksheet	324	340	347	666	174	263	247	301	514	190	726	412	273	482	304	455	6018
BP02-Deliv. Rm Manage.	324	340	347	72	174	263	247	285	67	190	95	412	273	482	304	455	4330
BP03-Outcome 1-7,10	1220	1320	1255	531	632	998	867	990	495	625	745	1483	1093	1782	1108	1772	16916
BP04-Outcome 14,21,28	869	928	845	192	458	716	644	713	171	444	262	1090	753	1217	856	1211	11369
BP05-Parente/Enter Intake	1150	1249	1195	362	555	828	776	755	352	550	527	1258	1180	1790	1121	1904	15552
BP07-Broncho. Dysplasia	317	340	347	666	173	262	246	281	514	187	724	410	273	482	303	455	5980
BP08A-Safety Data Form	38	25	53	18	3	20	56	41	49	50	11	41	18	62	17	42	544
BP08BASE-Oxy Reduc. BL	38	25	53	18	4	20	56	41	49	50	11	42	19	62	17	42	547
BP08BSTP-Oxy Reduc. Rep	347	216	471	218	36	186	502	399	441	450	101	402	150	558	153	378	5008
BP08RA-Room Air Phase	32	19	51	17	2	11	55	39	39	47	8	15	19	55	14	39	462
BP08RATP-Room Air Repeat	382	248	296	214	45	221	818	556	394	880	37	204	341	880	106	522	6144
BP08RDTP-Reduc. Repeat	637	427	474	175	68	326	1050	1765	1692	878	348	1020	314	1714	418	195	11501
BP08REDU-Reduc. Phase	107	73	72	25	11	55	172	287	295	148	59	170	55	289	76	31	1925
BP09-Acute Physiolo. II	322	341	347	74	174	263	247	277	67	190	95	412	273	482	303	455	4322
BP10-Therapeu. Interven.	441	475	456	205	225	357	305	351	192	225	284	534	388	651	384	635	6108
	6548	**6366**	**6609**	**3453**	**2734**	**4789**	**6288**	**7081**	**5331**	**5104**	**4033**	**7905**	**5422**	**10988**	**5484**	**8591**	**96726**

(All Forms Completed between 10/01/00 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.9A

Number of Infants Randomized in the Preemie INO Study
Status of Randomization by Center

						Number Reasons Not Consented					
Clinical Center	Number Screened	Number Eligible	Number Consented	Number Randomized	Percent Randomized/ Eligible	Not Med Eligible	Parent Refused Consent	Parent Unavail	Consent Not Sought	Other Reason	Reason Not Specified
4:Univ. of Texas (D)	129	44	36	36	81.82%	85	2	.	6	.	.
5:Wayne State Univ.	67	44	35	35	79.55%	23	3	.	6	.	.
9:Emory University	126	19	11	11	57.89%	107	0	.	8	.	.
11:Univ. of Cincinnati	326	48	30	30	62.50%	277	6	.	12	.	.
12:Indiana Univ.	324	71	36	35	49.30%	253	5	1	28	1	.
13:Yale University	242	43	20	19	44.19%	199	5	.	14	4	.
14:Brown University	664	51	43	42	82.35%	612	4	.	2	2	.
15:Stanford University	246	26	19	18	69.23%	220	3	1	3	.	.
16:Univ. of Alabama	226	74	45	44	59.46%	151	11	8	10	.	.
18:Univ. of Texas (H)	417	89	54	50	56.18%	328	15	1	16	3	.
20:Wake Forest	316	63	25	24	38.10%	253	10	2	19	7	.
21:Children's (NY)	217	19	6	6	31.58%	196	4	1	8	.	.
22:Univ. of Calif. at San Diego	204	28	23	23	82.14%	176	3	.	0	2	.
91:Univ. of Wisconsin	32	11	7	7	63.64%	21	0	.	4	.	.
92:Northwestern Univ.	124	26	20	20	76.92%	98	3	.	3	.	.
93:Univ. of Florida	443	67	50	51	76.12%	376	7	.	9	1	.
	4103	**723**	**460**	**451**	**62.38%**	**3375**	**81**	**14**	**148**	**20**	.

(All Forms Completed between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.9B

Number of Infants Randomized in the Preemie INO Study
Status of Randomization by Hospital Site

						Number Reasons Not Consented					
Hospital Site	Number Screened	Number Eligible	Number Consented	Number Randomized	Percent Randomized/ Eligible	Not Med Eligible	Parent Refused Consent	Parent Unavail	Consent Not Sought	Other Reason	Reason Not Specified
4:Parkland Hospital	129	44	36	36	81.82%	85	2	.	6	.	.
5:Children's Hospital of Michigan	4	2	2	2	100.00%	2	0	.	0	.	.
5:Hutzel Hospital	63	42	33	33	78.57%	21	3	.	6	.	.
9:Grady Memorial Hospital	126	19	11	11	57.89%	107	0	.	8	.	.
11:Univ. of Cincinnati Hospital	86	13	11	11	84.62%	73	1	.	1	.	.
11:Children's Hosp. Medical Center	32	7	6	6	85.71%	25	0	.	1	.	.
11:Good Samaritan Hospital	208	28	13	13	46.43%	179	5	.	10	.	.
12:University Hospital	8	3	2	2	66.67%	5	0	.	1	.	.
12:Riley Hospital for Children	270	52	25	24	46.15%	218	3	1	23	.	.
12:Methodist Hospital	46	16	9	9	56.25%	30	2	.	4	1	.
13:Yale-New Haven Hospital	242	43	20	19	44.19%	199	5	.	14	4	.
14:Women and Infants Hospital	664	51	43	42	82.35%	612	4	.	2	2	.
15:Children's Hosp. at Stanford	246	26	19	18	69.23%	220	3	1	3	.	.
16:University Hospital	226	74	45	44	59.46%	151	11	8	10	.	.
18:Memorial Hermann Children's Hospital	417	89	54	50	56.18%	328	15	1	16	3	.
20:Forsyth	234	50	22	21	42.00%	184	10	.	14	4	.
20:North Carolina Baptist	82	13	3	3	23.08%	69	0	2	5	3	.
21:University of Rochester	217	19	6	6	31.58%	196	4	1	8	.	.

(All Forms Completed between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.9B

Number of Infants Randomized in the Preemie INO Study
Status of Randomization by Hospital Site

						Number Reasons Not Consented					
Hospital Site	Number Screened	Number Eligible	Number Consented	Number Randomized	Percent Randomized/ Eligible	Not Med Eligible	Parent Refused Consent	Parent Unavail	Consent Not Sought	Other Reason	Reason Not Specified
22:U. of California-San Diego	91	17	15	15	88.24%	74	2	.	0	.	.
22:Sharp Mary Birch Hospital	113	11	8	8	72.73%	102	1	.	0	2	.
91:U. of Wisconsin	32	11	7	7	63.64%	21	0	.	4	.	.
92:Children's Memorial	41	7	4	4	57.14%	34	1	.	2	.	.
92:NW Memorial/Prentice	83	19	16	16	84.21%	64	2	.	1	.	.
93:Wolfson Children's	211	30	26	26	86.67%	181	3	.	1	.	.
93:Shads	232	37	24	25	67.57%	195	4	.	8	1	.
	4103	**723**	**460**	**451**	**62.38%**	**3375**	**81**	**14**	**148**	**20**	.

(All Forms Completed between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

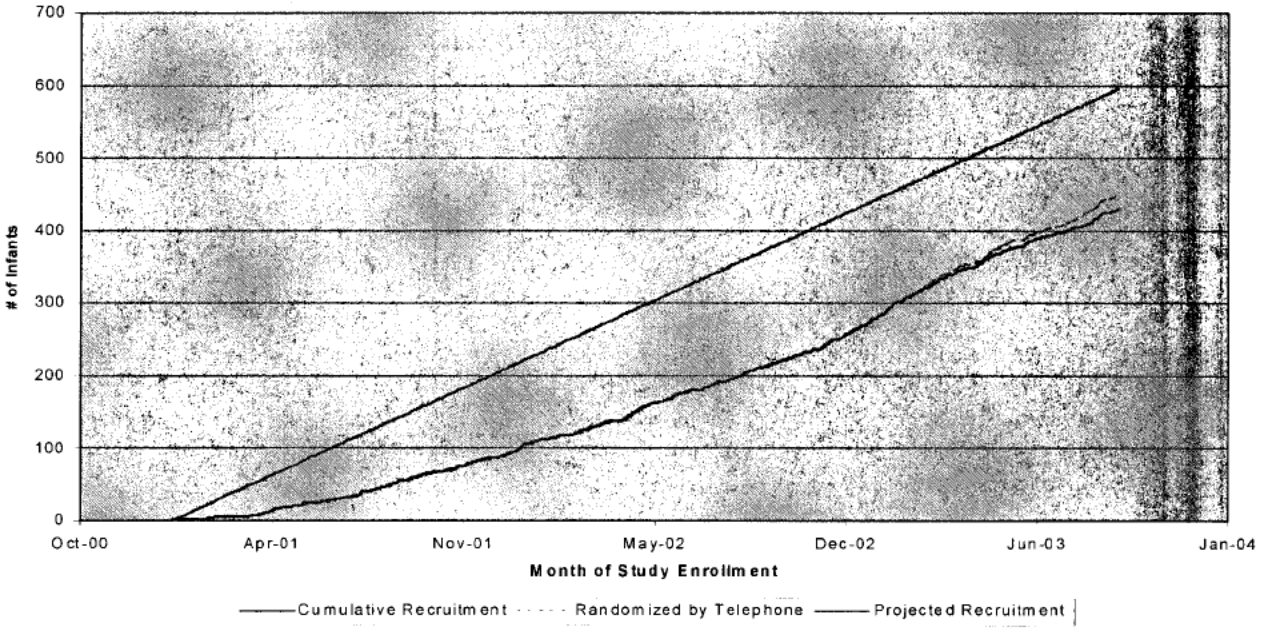
Table 2.9C

Number of Infants Randomized in the Preemie INO Study
By Birth Month and Center

	Birth Month	TX Dal.	WS	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	WF	NY	UCSD	WI	NW	FL	Total
*Data Files	Sep 2003	2	3	.	.	.	.	1	.	1	1	.	2	2	.	.	1	13
	Aug 2003	3	2	.	1	1	1	3	1	2	3	3	.	3	.	4	.	27
	Jul 2003	1	1	.	1	2	.	1	1	.	.	2	2	1	.	1	.	13
	Jun 2003	1	2	1	2	.	.	.	2	3	2	.	.	1	.	.	.	14
	May 2003	5	3	.	1	.	2	5	.	3	3	2	.	1	.	1	.	26
	Apr 2003	.	1	1	.	2	.	1	.	1	5	2	.	.	.	.	.	13
	Jan-Mar 2003	3	8	2	8	4	2	12	2	4	9	4	2	7	.	1	6	74
	2002	13	10	7	16	19	7	10	8	22	17	10	.	8	5	6	16	174
	2001	8	5	.	1	7	7	9	4	8	10	1	.	.	2	7	28	97
		36	**35**	**11**	**30**	**35**	**19**	**42**	**18**	**44**	**50**	**24**	**6**	**23**	**7**	**20**	**51**	**451**
**Telephone Rand System	Sep 2003	2	3	.	.	.	.	1	.	1	1	2	2	2	.	.	1	15
	Aug 2003	3	2	.	1	1	1	3	1	2	3	1	.	3	.	4	.	25
	Jul 2003	1	1	.	1	2	.	1	1	.	.	2	2	1	.	1	.	13
	Jun 2003	1	2	1	2	.	.	.	2	3	2	.	.	1	.	.	.	14
	May 2003	5	3	.	1	.	2	5	.	3	3	2	.	1	.	1	.	26
	Apr 2003	.	1	1	.	2	.	1	.	1	5	3	.	.	.	.	.	14
	Jan-Mar 2003	3	8	2	8	4	2	12	2	4	10	3	2	7	.	1	6	74
	2002	13	11	7	16	19	7	10	8	22	17	10	.	8	5	6	16	175
	2001	8	4	.	1	7	7	9	4	8	9	1	.	.	2	7	28	95
		36	**35**	**11**	**30**	**35**	**19**	**42**	**18**	**44**	**50**	**24**	**6**	**23**	**7**	**20**	**51**	**451**

(All Forms Completed between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PN01, PN02 and randomization system.
** Non-Network sites are University of Florida, Northwestern University and University of Wisconsin. These forms are keyed centrally.*

Table 2.9.D
Enrollment in the Preemie INO Study



NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.9E

Number of Forms in the Preemie INO Study
By Form Type and Center

	Clinical Center																
Form Type	TX Dal.	WS	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	WF	NY	UCSD	WI *	NW *	FL *	Total
PN01-Screening Log	129	67	126	328	324	242	664	246	226	417	316	217	205	32	124	444	4107
PN02-Eligibility	49	44	33	74	86	55	55	41	93	99	73	22	56	12	36	72	900
PN03-Baseline	36	35	11	30	35	19	42	18	44	50	24	6	23	7	20	50	450
PN04-Gas Response	36	35	11	30	35	19	42	18	44	50	24	6	23	7	20	50	450
PN05-Safety Monitor	38	39	11	32	36	23	45	18	44	55	25	6	24	7	20	52	475
PN06-Treat/Morbidity	36	35	11	30	35	19	42	18	44	50	24	6	23	7	20	50	450
PN07-Outcome	36	35	11	30	35	19	42	18	44	50	24	6	23	7	20	51	451
PN09-Echocardiogram	.	.	.	.	5	2	.	6	.	.	.	.	.	.	.	.	13
PN10-Baseline/Outcome	9	7	8	21	36	25	10	9	32	40	40	13	5	4	1	13	273
PN11-Neuroimaging	36	35	11	30	35	19	42	18	44	50	24	6	23	7	20	50	450
	405	**332**	**233**	**605**	**662**	**442**	**984**	**410**	**615**	**861**	**574**	**288**	**405**	**90**	**281**	**832**	**8019**

(All Forms Completed between 01/01/01 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

** Non-Network sites are University of Florida, Northwestern University and University of Wisconsin. These forms are keyed centrally.*

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.12A

Number of Infants Randomized in the Phototherapy Study
Status of Randomization by Center

Clinical Center	Number Potentially Enrollable+	Number Eligible for Screening*	Number Screened	Number Ineligible	Number Eligible	Number Randomized	Percent Randomized (Randomised/ Eligible)	Percent Randomized (Randomised/ Potentially Enrollable)	Consent Granted (Not Randomized)	Parent Unavail	Parent Refused Consent	Consent Not Requested	Physician Refused Consent	Other
3: CW	235	237	156	24	132	100	75.76%	42.55%	0	0	22	5	2	3
4: TX Dal.	194	196	134	14	120	108	90.00%	55.67%	0	0	11	1	0	0
5: WS	356	358	167	18	149	113	75.84%	31.74%	0	5	22	4	3	2
8: MI	414	428	276	58	218	181	83.03%	43.72%	1	2	30	2	0	2
9: EM	279	296	201	67	134	90	67.16%	32.26%	0	2	40	2	0	0
11: CN	490	489	318	72	246	115	46.75%	23.47%	1	1	85	39	2	3
12: IN	409	409	281	51	230	150	65.22%	36.67%	2	2	26	36	6	8
13: YL	305	293	182	45	137	81	59.12%	26.56%	0	1	47	4	2	2
14: BR	333	326	205	17	188	152	80.85%	45.65%	0	2	23	7	4	0
15: ST	176	185	130	36	94	58	61.70%	32.95%	0	3	26	3	0	4
16: AL	526	521	343	36	307	237	77.20%	45.06%	0	23	38	3	1	5
18: TX Hstn.	528	536	313	47	266	199	74.81%	37.69%	0	7	57	2	0	1
19: DU	245	241	143	31	112	76	67.86%	31.02%	0	5	13	16	2	0
20: WF	365	399	278	59	219	129	58.90%	35.34%	0	6	46	23	4	11
21: NY	187	173	124	15	109	61	55.96%	32.62%	0	6	37	3	1	1
22: UCSD	393	395	258	46	212	124	58.49%	31.55%	0	11	58	8	8	3
	5435	**5482**	**3509**	**636**	**2873**	**1974**	**68.71%**	**36.32%**	**4**	**76**	**581**	**158**	**35**	**45**

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PHT02 and NG02.

** Eligibility for screening determined by the following four conditions:*
1) alive at 12 hours after birth, 2) birth weight is under 1000 grams
3) if outborn, admitted to NICU within 36 hours of birth, 4) born on or after 12/01/02 or 7/01/03 for center=5 and site='C'
+ Potentially Enrollable determined by the following conditions:
1) Eligible for screening but was not screened OR 2) Has received Phototherapy prior to Randomization OR
3) Is Eligible (i.e. Q B.1 = 1,2,3,4,5, or 6)

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

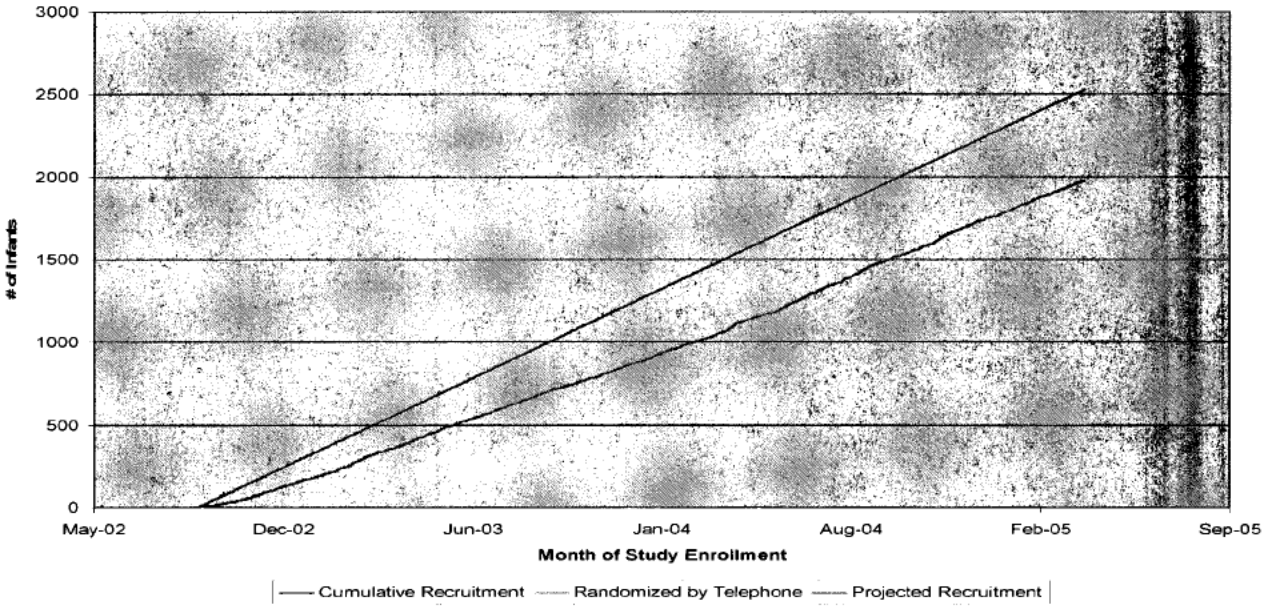
Table 2.12B

Number of Infants Randomized in the Phototherapy Study
By Randomization Month and Center

		Clinical Center																
	Randomization Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
*Data Files	Apr 2005	2	.	.	.	.	1	2	1	.	.	.	.	.	.	.	1	7
	Mar 2005	.	5	4	4	7	1	2	6	2	3	14	13	4	6	3	.	74
	Feb 2005	2	1	5	7	3	3	6	5	7	2	3	3	5	3	2	5	62
	Jan 2005	3	3	7	9	1	6	7	1	3	4	5	7	1	4	3	7	71
	2004	54	58	55	64	34	55	65	31	80	16	102	71	29	59	21	65	859
	2003	38	34	36	78	34	34	52	29	51	29	89	86	27	51	24	42	734
	2002	1	7	6	19	11	15	16	8	9	4	24	19	10	6	8	4	167
		100	**108**	**113**	**181**	**90**	**115**	**150**	**81**	**152**	**58**	**237**	**199**	**76**	**129**	**61**	**124**	**1974**
**Telephone Rand System	Apr 2005	2	.	.	.	.	1	2	1	.	.	.	.	.	.	.	2	8
	Mar 2005	.	5	4	4	7	1	2	6	2	3	14	13	4	6	3	.	74
	Feb 2005	2	2	5	7	3	3	6	5	7	2	3	3	5	3	2	5	63
	Jan 2005	3	3	7	9	1	6	7	1	3	4	5	7	1	4	3	7	71
	2004	54	58	55	64	34	55	65	31	80	16	102	71	30	59	21	65	860
	2003	38	34	36	78	34	34	52	29	51	29	89	86	27	51	24	42	734
	2002	1	7	6	19	11	15	16	8	9	4	24	19	10	6	8	4	167
		100	**109**	**113**	**181**	**90**	**115**	**150**	**81**	**152**	**58**	**237**	**199**	**77**	**129**	**61**	**125**	**1977**

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PHT01 and PHT02.

Table 2.12C Enrollment in the Phototherapy Study



NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.12D

Number of Forms in the Phototherapy Study
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
PHT01-Screening Log	156	134	167	276	201	318	281	180	205	130	343	313	143	278	124	258	3507
PHT02-Eligibility	156	134	167	276	201	318	281	182	205	130	343	313	143	278	124	258	3509
PHT03-Laboratory Level	100	109	111	181	90	115	150	81	152	58	237	199	76	129	61	124	1973
PHT04-Daily Worksheet	1369	1434	1357	2412	1160	1562	1981	1109	2057	754	3202	2505	1019	1741	849	1592	26103
PHT05-Exchange Transfu	.	.	7	3	1	1	.	.	.	.	1	.	1	2	1	.	17
PHT06-Prot. Violation	41	52	81	222	39	65	75	41	40	12	121	55	56	78	59	33	1070
PHT08-Specimen Ship	100	95	71	159	77	96	49	41	132	48	201	160	48	87	39	116	1519
PHT10-Hearing Assess.	100	109	112	270	90	115	150	81	152	58	237	199	76	129	61	124	2063
	2022	**2067**	**2073**	**3799**	**1859**	**2590**	**2967**	**1715**	**2943**	**1190**	**4685**	**3744**	**1562**	**2722**	**1318**	**2505**	**39761**

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.12E

Number of Forms in the Phototherapy Secondary Study - BAER
By Form Type and Center

Form Type	WS	MI	IN	BR	TX Hstn.	NY	Total
BAER01-Eligibility	86	117	40	69	121	57	490
BAER02-Recording	59	22	4	54	93	40	272

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.12F

Number of Infants Randomized in the Phototherapy Study
Status of the Unbound Bilirubin Study

Clinical Center	Number Randomized	Number with PHT08	Number with UBC sample drawn	Number Consented for UB Study	Number Exchanged Transfusion with PHT05
3:Case Western Univ.	100	100	79	88	0
4:Univ. of Texas (D)	108	95	90	102	0
5:Wayne State Univ.	113	71	60	75	2
8:Univ. of Miami	181	159	122	153	0
9:Emory University	90	77	68	77	0
11:Univ. of Cincinnati	115	96	73	79	1
12:Indiana Univ.	150	49	42	48	0
13:Yale University	81	41	38	39	0
14:Brown University	152	132	130	141	0
15:Stanford University	58	48	43	49	0
16:Univ. of Alabama	237	201	193	198	0
18:Univ. of Texas (H)	199	160	138	151	0
19:Duke University	76	47	45	58	0
20:Wake Forest	129	87	83	88	1
21:Children's (NY)	61	39	39	39	1
22:Univ. of Calif. at San Diego	124	116	91	105	0
	1974	**1518**	**1334**	**1490**	**5**

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PHT02 and PHT08.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.13A

Number of Infants Enrolled in the Candidiasis Study
Status of Enrollement by Center

Clinical Center	Number Eligible for Screening*	Number Screened	Number Eligible	Number** Enrolled	Number Positive Blood Culture	Consent Granted	Parent Unavail	Parent Refused Consent	Consent Not Requested	Physician Refused Consent	Other	Multi Study Participation
3:Case Western Univ.	161	150	138	60	1	65	18	43	9	2	1	0
4:Univ. of Texas (D)	125	122	122	78	1	96	0	22	2	1	1	0
5:Wayne State Univ.	131	76	72	39	10	41	0	28	2	0	1	0
8:Univ. of Miami	214	141	141	77	15	84	19	37	0	0	1	0
9:Emory University	212	187	186	65	2	69	20	83	13	0	1	0
11:Univ. of Cincinnati	291	245	244	74	2	102	8	104	26	1	2	1
12:Indiana Univ.	261	235	232	19	2	21	13	158	5	11	9	15
13:Yale University	179	139	139	42	5	55	5	42	30	3	4	0
14:Brown University	199	197	197	107	8	135	0	42	2	5	1	12
15:Stanford University	136	116	112	32	0	49	11	31	13	2	6	0
16:Univ. of Alabama	336	312	311	160	7	180	18	94	2	3	13	1
18:Univ. of Texas (H)	304	245	245	88	10	134	7	93	2	1	8	0
19:Duke University	174	156	156	63	3	75	3	69	6	0	3	0
20:Wake Forest	95	39	35	8	0	8	14	3	6	0	4	0
21:Children's (NY)	108	105	103	23	3	25	2	58	3	3	12	0
22:Univ. of Calif. at San Diego	260	240	234	84	5	95	10	94	20	2	11	2
	3186	**2705**	**2667**	**1019**	**74**	**1234**	**148**	**1001**	**141**	**34**	**78**	**31**

(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the CA02.

*** This column is based on at least one culture obtained after 72 hours of age.*
** Eligibility for screening determined by the following two conditions:*
1) Birth weight is <= 1000 grams.
2) Alive at =>72 hours.
Note: Eligibility for screening determined by NG02 and NG03 and number screened determined by CA02.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.13B

Number of Forms in the Candidiasis Study
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
CA01-Screening Log	164	123	77	147	191	265	247	145	197	118	320	260	166	39	110	250	2819
CA02-Eligibility	154	123	77	147	191	264	241	139	197	118	320	260	163	39	109	247	2789
CA03-Clinical Evaluation	213	369	50	429	319	240	130	158	393	145	844	498	311	37	242	362	4740
CA04-Candidiasis Positive	3	5	1	16	2	4	2	5	8	.	15	11	4	.	1	8	85
CA05-Culture Report Form	551	1210	143	1281	458	369	207	510	807	361	1407	1021	707	114	365	993	10504
CA06-Culture Therapy	397	792	77	754	484	521	220	391	735	301	1280	740	578	108	201	692	8271
CA07-Specimen Form	42	70	.	37	52	52	12	34	90	28	121	62	47	7	6	59	719
CA08-Isolate Specimen Form	2	4	.	1	3	2	.	5	7	.	8	11	2	.	2	8	55

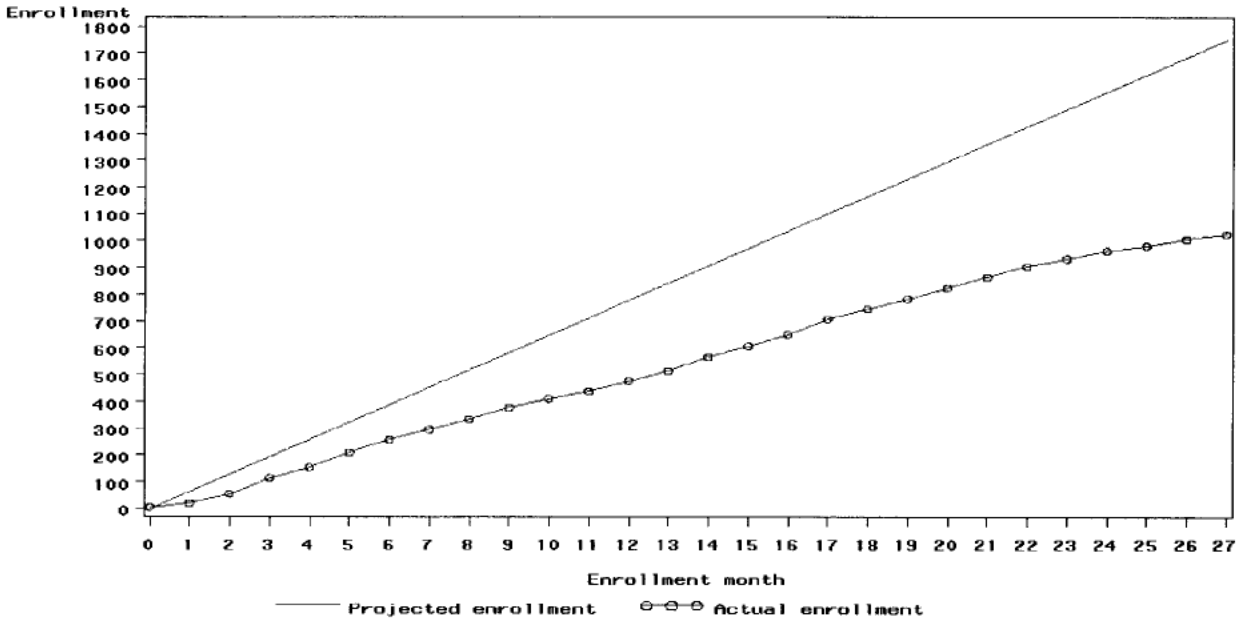
(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.13C

Projected and Actual Candida Enrollment Through March 2006



Projected enrollment is based on 27 month enrollment period, starting in April 2004

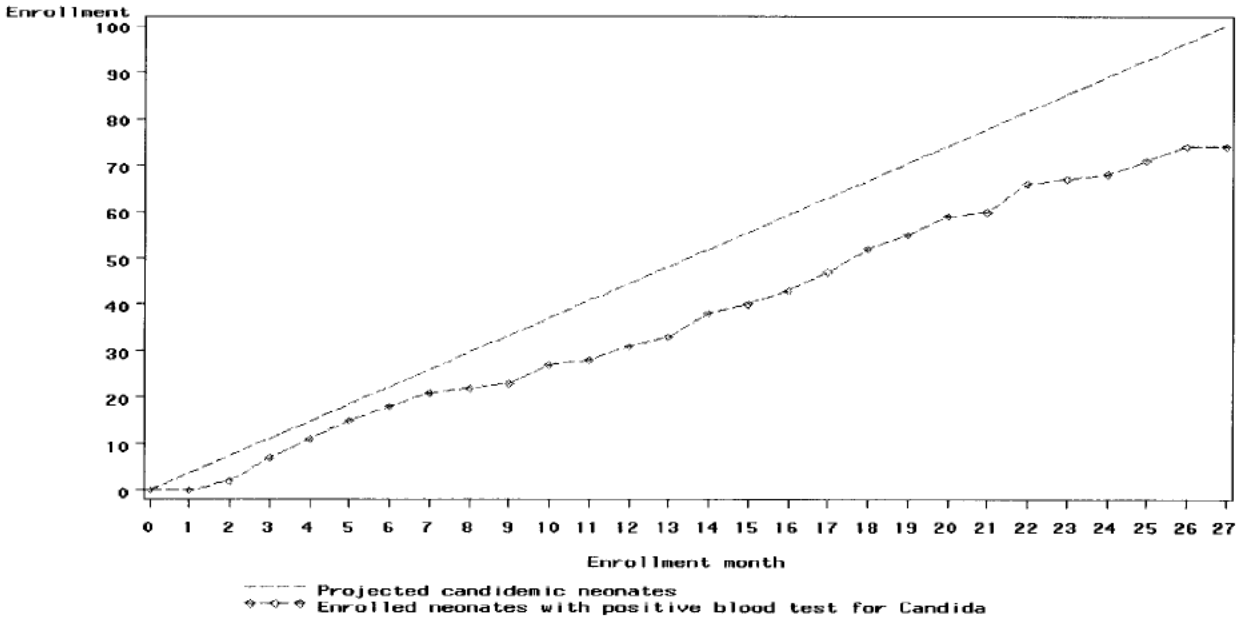
(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.13D

Projected and Actual Candida Neonates Through March 2006



Projected enrollment is based on 27 month enrollment period, starting in April 2004

(All Forms Completed between 03/01/04 and 06/30/06 · Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.14A

Number of Infants Enrolled in the New aEEG Study
Status of Enrollment by Center

Clinical Center	Number Screened	Number Ineligible	Number Eligible	Number Enrolled	Percent Enrolled (Enrolled/ Eligible)	Consent Granted (Not Enrolled)	Parent Refused Consent	Physician Refused Consent	Consent Not Requested	Buccal Smear Obtained (Question A1.=Yes on AE12)	Number Infants Cooled (Question B1=Yes on AE05)
3:Case Western Univ.	33	24	9	8	88.89%	0	0	0	1	8	6
4:Univ. of Texas (D)	83	49	34	27	79.41%	0	3	0	5	23	5
5:Wayne State Univ.	12	5	7	7	100.00%	0	0	0	0	0	4
8:Univ. of Miami	2	0	2	2	100.00%	0	0	0	0	0	0
9:Emory University	14	12	2	2	100.00%	0	0	0	0	0	0
12:Indiana Univ.	16	8	8	8	100.00%	0	0	0	0	0	6
13:Yale University	17	10	7	7	100.00%	0	0	0	0	4	6
14:Brown University	54	44	10	10	100.00%	0	0	0	0	4	3
15:Stanford University	9	9	0	0	.	0	0	0	0	0	0
16:Univ. of Alabama	10	2	8	8	100.00%	0	0	0	0	6	4
18:Univ. of Texas (H)	22	14	8	8	100.00%	0	0	0	1	6	7
19:Duke University	14	6	8	8	100.00%	1	0	0	0	7	6
20:Wake Forest	5	4	1	1	100.00%	0	0	0	0	1	1
21:Children's (NY)	7	2	5	5	100.00%	0	0	0	0	5	3
22:Univ. of Calif. at San Diego	5	4	1	1	100.00%	0	0	0	0	0	0
	303	**193**	**110**	**102**	**92.73%**	**1**	**3**	**0**	**7**	**64**	**51**

(All Forms Completed between 09/01/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the AE01, AE02, AE05 and AE12.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.14B

Number of Forms in the aEEG Study
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
AE01-Screening Log	32	81	12	2	14	16	16	54	9	10	21	14	5	7	5	298
AE02-Eligibility	32	81	11	2	14	16	16	54	9	10	21	14	5	7	5	297
AE03-Maternal Baseline	7	25	6	2	2	8	6	10	.	8	7	9	1	5	1	97
AE04-Neonatal Information	7	25	6	2	2	8	6	10	.	8	7	9	1	5	1	97
AE05-aEEG Recording Form	8	27	7	2	2	8	7	10	.	8	8	9	1	5	1	103
AE06-Data During 72 Hrs	7	25	2	2	2	8	6	10	.	8	7	9	1	5	1	93
AE08-Imaging Studies	7	25	4	2	2	8	6	10	.	8	7	9	1	5	1	95
AE09-Status Form	7	25	2	2	2	8	6	10	.	8	7	9	.	5	1	92
AE10-Discharge Diagnosis	7	25	2	2	2	8	6	10	.	8	7	9	.	5	1	92
AE11-Protocol Violation	2	10	.	.	.	.	.	.	.	.	.	2	.	.	.	14
AE12-Buccal Smear Coll.	7	24	.	.	.	2	6	4	.	8	5	8	1	5	1	71
	123	**373**	**52**	**18**	**42**	**90**	**81**	**182**	**18**	**84**	**97**	**101**	**16**	**54**	**18**	**1349**

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.15A

Enrollment Tracking Report in the PCV-7 Study
By Weight Group

						Number Enrolled			
Weight Group	Enrollment Status	Enrollment Target	Number Enrolled	In Window 2nd Shot	In Window 3rd Shot	Successful* Completion	Not in** Window	Still*** Pending	Potential**** Enrollment
401-500	Open	40	5	5	5	5	0	0	0
501-600	Open	40	17	15	15	13	1	3	0
601-700	Open	40	27	25	20	16	5	6	0
701-800	Suspended	40	38	32	28	18	14	6	0
801-900	Completed	40	41	37	32	20	16	5	0
901-1000	Completed	40	48	47	37	25	14	9	0
1001-1100	Completed	40	39	38	35	27	9	3	0
1101-1200	Completed	40	41	38	36	27	14	0	0
1201-1300	Completed	40	34	32	27	22	6	6	0
1301-1400	Suspended	40	35	29	22	17	9	9	0
1401-1500	Open	40	19	17	16	13	5	1	1
		440	**344**	**315**	**273**	**203**	**93**	**48**	**1**

(All Forms Completed between 07/06/02 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PCV7.
** Successful Completion: cases in the Primary Outcome Group (all shots and blood draw in their windows).*
*** Not In Window: cases that failed to make the Primary Outcome Group. These include missed shots/blood draw or shot/blood draw out of window.*
**** Still Pending: cases that are in window but have not yet had all of the shots or the blood draw.*
***** Potential Enrollment: cases that are consented but have not yet had their first shot and therefore are not enrolled.*

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.15B

Number of Infants Enrolled in the PCV7 Study
By Center

	Clinical Center									
Weight Group	TX Dal.	WS	MI	EM	ST	AL	DU	WF	NY	Total
401-500	2	1	.	.	.	.	.	1	1	5
501-600	3	.	.	.	.	3	.	7	4	17
601-700	5	3	2	.	.	7	.	5	5	27
701-800	7	5	3	2	.	3	4	10	4	38
801-900	12	3	7	1	1	5	.	8	4	41
901-1000	12	6	5	4	.	2	2	6	11	48
1001-1100	14	3	4	2	.	1	2	8	5	39
1101-1200	21	1	2	3	1	1	.	4	8	41
1201-1300	16	4	.	.	.	2	1	4	7	34
1301-1400	13	1	5	1	1	2	2	3	7	35
1401-1500	6	1	.	1	.	2	.	2	7	19
	111	**28**	**28**	**14**	**3**	**28**	**11**	**58**	**63**	**344**

(All Forms Completed between 07/06/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PC701.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.15C

Number of Infants Enrolled in the PCV-7 Study
Status of Enrollment by Center

Clinical Center	Number Potentially Elig Screened *1	Number Actually Elig Screened *2	Number Screened *3	Number Alive Cathment Area	Number Eligible *4	Number Enrolled *5	Consent Granted	Parent Refused Consent	Consent Not Sought	Parent Unavail	Other	Hold On Weight
4:Univ. of Texas (D)	326	295	133	132	121	114	114	2	5	0	0	1
5:Wayne State Univ.	271	233	35	35	33	31	31	2	0	0	0	0
8:Univ. of Miami	347	314	112	112	62	37	37	19	0	4	2	0
9:Emory University	416	371	122	49	27	19	19	7	0	0	1	6
15:Stanford University	276	254	195	16	7	3	3	2	1	0	1	5
16:Univ. of Alabama	615	556	75	73	53	28	28	21	0	4	0	2
19:Duke University	226	203	11	11	11	11	11	0	0	0	0	0
20:Wake Forest	500	446	257	199	101	58	58	14	6	22	1	27
21:Children's (NY)	244	228	219	213	171	63	63	77	2	3	26	18
	3221	**2900**	**1159**	**840**	**586**	**364**	**364**	**144**	**14**	**33**	**31**	**59**

(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the NG02, NG03, PC701 and PC702.

**1 The form NG02 completed, gestational age at birth < 32 wks and alive at 12 hours of age.*
**2 Meets the condition *1 and did not die before 28 days of life based on NG03.*
**3 Meets the condition *2 and the form PCV01 completed.*
**4 The form PC702 completed and consent status other than 0 (Not Eligible).*
**5 Consented and received the first PCV-7 dose within the shot window.*

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.15D

Number of Forms in the PCV7 Study
By Form Type and Center

Form Type	TX Dal.	WS	MI	EM	ST	AL	DU	WF	NY	Total
PC701-Screening Log	136	35	120	143	195	76	11	268	225	1209
PC702-Eligibility	136	34	119	55	13	73	11	219	222	882
PC703-Immunization Status	112	11	35	13	2	23	8	57	62	323
PC704-Adverse Event	7	4	2	2	.	8	1	31	23	78
	391	**84**	**276**	**213**	**210**	**180**	**31**	**575**	**532**	**2492**

(All Forms Completed between 07/06/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.15E

Number of Infants Enrolled in the Hib Secondary (PCV-7)
Status of Enrollment by Center

Clinical Center	Number Receiving Merck Pedvax or Comvax (PRP-OMP) First Dose	Number Receiving Merck Pedvax or Comvax (PRP-OMP) Second Dose	Number Enrolled	Parent Refused Consent	Consent Not Sought	Parent Unavail	Other (Reason)	Number Completing Study Visit Blood Draw
16:Univ. of Alabama	1	0	0	1	0	0	0	0
21:Children's (NY)	20	20	12	6	1	1	0	12
	21	**20**	**12**	**7**	**1**	**1**	**0**	**12**

(All Forms Completed between 07/??/05 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the HIB03 and HIB03D.

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Table 2.15F

Number of Forms in the HIB Secondary (PCV-7)
By Form Type and Center

Form Type	AL	NY	Total
HIB03-Immun. Tracking	20	20	40
	20	**20**	**40**

(All Forms Completed between 07/06/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

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Table 2.15G

Number of Infants Enrolled in the NP Secondary (PCV-7) by enrollment status and center

Clinical Center	Number Of Infants Consenting for the NP Study	Number Enrolled	Swab # 1 Obtained	Swab # 2 Obtained	Number Positive for Streptococcus pneumoniae	Number Positive Swab 1	Number Positive Swab 2
4:Univ. of Texas (D)	18	5	5	0	0	0	0
5:Wayne State Univ.	33	25	24	8	3	2	1
8:Univ. of Miami	5	0	0	0	0	0	0
16:Univ. of Alabama	28	16	15	13	0	0	0
19:Duke University	2	0	1	0	0	0	0
21:Children's (NY)	69	67	42	26	5	0	5
	155	**113**	**87**	**47**	**8**	**2**	**6**

(All Forms Completed between 07/??/05 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the PC702 and NP01.

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Monthly Report for the Period Ending 06/30/06

Table 2.15H

Number of Forms in the NP Secondary (PCV-7)
By Form Type and Center

Form Type	TX Dal.	WS	AL	DU	NY	Total
NP01-NP Swab Collection Form	5	32	31	1	68	137
NP03-Risk Assess. Questionnaire	4	3	13	.	23	43
	9	**35**	**44**	**1**	**91**	**180**

(All Forms Completed between 07/06/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.16A

Number of Infants Enrolled in the New Pilot Study for the Oxygenation Trial in ELBW Infants
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 Unavailable	Parent Refused Consent	Consent Not Requested	Physician Refused Consent	Research Personnel Unavailable
3:Case Western Univ.	4	1	3	3	100.00%	0	0	0	0	0	0
8:Univ. of Miami	3	1	2	2	100.00%	0	0	0	0	0	0
11:Univ. of Cincinnati	1	0	1	1	100.00%	0	0	0	0	0	0
16:Univ. of Alabama	16	5	11	10	90.91%	0	0	1	0	0	0
22:Univ. of Calif. at San Diego	.	.	.	.	.	.	.	.	.	.	.
	24	**7**	**17**	**16**	**94.12%**	**0**	**0**	**1**	**0**	**0**	**0**

(All Forms Completed between 11/01/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the AE01, AE02 and AE12.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.16B

Number of Infants Randomized in the Pilot Study for the Oxygenation Trial in ELBW Infants
By Randomization Month and Center

	Clinical Center				
Randomization Month	CW	MI	CN	AL	Total
May 2005	.	.	1	.	1
Mar 2005	.	.	.	3	3
Feb 2005	.	.	.	1	1
Jan 2005	.	1	.	1	2
Dec 2004	1	1	.	3	5
Nov 2004	2	.	.	2	4
	3	**2**	**1**	**10**	**16**

(All Forms Completed between 11/01/05 and 06/30/06 · Table Produced on 07/11/06)
The table is generated from the PLT02.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.16C

Number of Forms in the Pilot Study for the Oxygenation Trial in ELBW Infants
By Form Type and Center

Form Type	CW	MI	CN	AL	Total
PLT01-Screening Log	4	3	1	16	24
PLT02-Eligibility/Baseline	3	2	1	14	20
PLT03-Daily Outcome Form	9	9	3	33	54
	16	**14**	**5**	**63**	**98**

(All Forms Completed between 11/01/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

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 Unavailable	Parent Refused Consent	Consent Not Requested	Physician Refused Consent
3:Case Western Univ.	71	3	68	40	58.82%	2	1	5	20	0
4:Univ. of Texas (D)	31	12	19	15	78.95%	0	0	2	2	0
5:Wayne State Univ.	4	0	4	4	100.00%	0	0	0	0	0
8:Univ. of Miami	33	1	32	17	53.13%	2	2	9	2	0
9:Emory University	55	9	46	22	47.83%	0	1	9	14	0
11:Univ. of Cincinnati	91	5	86	20	23.26%	1	21	34	10	0
12:Indiana Univ.	32	7	25	16	64.00%	0	3	5	1	0
13:Yale University	38	2	36	3	8.33%	1	7	8	17	0
14:Brown University	75	25	50	33	66.00%	1	0	11	4	1
15:Stanford University	7	1	6	4	66.67%	0	0	2	0	0
16:Univ. of Alabama	78	6	72	40	55.56%	7	0	19	6	0
18:Univ. of Texas (H)	47	2	45	26	57.78%	2	1	6	10	0
19:Duke University	33	5	28	16	57.14%	0	1	10	1	0
20:Wake Forest	20	0	20	9	45.00%	0	1	5	5	0
21:Children's (NY)	29	21	8	8	100.00%	0	0	0	0	0
22:Univ. of Calif. at San Diego	94	18	76	43	56.58%	0	12	12	9	0
	738	**117**	**621**	**316**	**50.89%**	**16**	**50**	**137**	**101**	**1**

(All Forms Completed between 11/01/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the SUPP01 and SUPP02.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17B

Number of Infants Randomized in the SUPPORT Trial
By Randomization Month and Center

	Clinical Center																
Randomization Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
Jun 2006	1	3	1	.	4	1	2	1	7	.	2	1	.	.	.	.	23
May 2006	4	1	.	.	1	.	4	1	2	1	.	1	1	.	.	.	16
Apr 2006	6	1	1	.	3	.	.	.	2	1	.	5	.	.	.	.	19
Mar 2006	5	.	2	.	.	.	.	.	.	.	.	.	.	.	1	.	8
Feb 2006	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	2	2
Nov 2005	.	.	.	2	4	.	.	.	.	.	4	2	.	3	.	1	16
Oct 2005	1	3	.	1	1	3	1	.	3	.	5	4	2	3	2	4	33
Sep 2005	1	.	.	2	1	1	.	.	4	.	3	1	5	3	3	4	28
Aug 2005	9	4	.	5	.	3	3	.	.	.	5	.	2	.	2	8	41
Jul 2005	3	3	.	3	3	3	.	.	4	.	5	1	1	.	.	4	30
Jun 2005	5	.	.	1	3	4	2	1	3	.	12	1	2	.	.	7	41
May 2005	4	.	.	3	1	2	1	.	1	2	2	5	3	.	.	7	31
Apr 2005	1	.	.	.	.	1	2	.	3	.	.	1	.	.	.	.	8
Mar 2005	.	.	.	.	.	2	1	.	3	.	2	4	.	.	.	4	16
Feb 2005	.	.	.	.	.	.	.	.	1	.	.	.	.	.	.	2	3
Q .	.	.	.	.	1	.	.	.	.	.	.	.	.	.	.	.	1
	40	**15**	**4**	**17**	**22**	**20**	**16**	**3**	**33**	**4**	**40**	**26**	**16**	**9**	**8**	**43**	**316**

(All Forms Completed between 11/01/05 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the SUPP01 and SUPP02.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17C

Number of Forms in the Support Trial
By Form Type and Center

Form Type	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
SUPP01-Screening Log	71	31	4	33	55	91	32	38	75	7	78	47	33	20	29	94	738
SUPP02-Eligibility Form	71	28	4	33	51	91	28	36	75	6	78	46	32	20	8	79	686
SUPP03-Delivery Form	40	15	3	17	22	20	13	3	33	4	40	26	16	9	7	43	311
SUPP04-NICU Admission	37	15	3	17	21	20	13	3	32	4	40	26	17	9	7	43	307
SUPP05-Safety Monitoring	521	151	.	238	277	252	170	42	400	56	482	247	197	126	98	533	3790
SUPP05A- (Supplemental)	29	3	.	.	10	2	6	1	8	4	1	14	1	1	1	1	82
SUPP06-Protocol Violation	8	4	.	.	1	11	1	.	6	.	11	4	.	3	2	6	57
SUPP07-Reintubation	71	20	.	37	49	22	16	.	113	4	20	31	12	24	18	25	462
SUPP08-Adverse Event	9	5	.	4	4	13	1	.	26	.	37	2	8	9	2	26	146
SUPP09-Outcome Status	23	10	.	17	14	19	11	1	23	2	37	20	14	9	7	42	249
SUPP10-SUPP10	112	48	.	78	56	43	65	3	136	12	97	99	34	46	33	261	1123
SUPP11-SUPP11	1820	494	.	705	856	657	552	81	1366	72	1488	933	521	550	287	1734	12116
	2812	**824**	**14**	**1179**	**1416**	**1241**	**908**	**208**	**2293**	**171**	**2409**	**1495**	**885**	**826**	**499**	**2887**	**20067**

(All Forms Completed between 11/01/04 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17D

Number of Mothers Enrolled in the Antenatal Consent Secondary Study
Status of Enrollement by Center

Clinical Center	Number Screened*	Number Approached**	Number of Consents Obtained***
3:Case Western Univ.	10	8	4
4:Univ. of Texas (D)	11	11	9
5:Wayne State Univ.	.	.	.
8:Univ. of Miami	.	.	.
9:Emory University	44	40	20
11:Univ. of Cincinnati	29	27	7
12:Indiana Univ.	14	8	4
13:Yale University	30	23	12
14:Brown University	65	55	40
15:Stanford University	5	4	2
16:Univ. of Alabama	19	11	8
18:Univ. of Texas (H)	.	.	.
19:Duke University	60	51	20
20:Wake Forest	.	.	.
21:Children's (NY)	.	.	.
22:Univ. of Calif. at San Diego	14	12	4
	301	**250**	**130**

(All Forms Completed between 03/01/04 and 06/30/06 - Table Produced on 07/11/06)

** Number of unique screening IDs in the Ant01.*
*** Ant02 forms with Q. 1 = 'Y'.*
**** Number of consents obtained based on above criteria and ANT02 Q. 8 = 'Y'.*

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17E

Number of Forms in the Anenatal Consent Secondary Study
By Form Type and Center

Form Type	CW	TX Dal.	EM	CN	IN	YL	BR	ST	AL	DU	UCSD	Total
ANT01-Screening Log	10	13	47	32	16	34	75	5	21	67	18	338
ANT02-Screen and Consent	10	11	43	30	13	29	65	5	18	58	14	296
	20	**24**	**90**	**62**	**29**	**63**	**140**	**10**	**39**	**125**	**32**	**634**

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17F

Number of Infants enrolled in the Neuroimaging and Neurodevelopmental Outcomes Secondary (SUPPORT) Status of Enrollement by Center

Clinical Center	Number Enrolled	Number Early Cranial US	Number of Late Cranial US	Number of Brain MRIs
15:Stanford University	2	2	0	2
22:Univ. of Calif. at San Diego	9	11	9	7
	11	**13**	**9**	**9**

(All Forms Completed between 11/01/04 and 06/30/06 - Table Produced on 07/11/06)
The table is generated from the MRI01.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17G

Number of Forms in the Neuroimaging and Neurodevelopmental Outcomes Secondary (SUPPORT)
By Form Type and Center

Form Type	ST	UCSD	Total
MRI01-Enrollment/Tracking/Local#Reader Form	2	11	13
	2	**11**	**13**

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17H

Number of Forms in the Post-natal Growth Secondary (SUPPORT)
By Form Type and Center

Form Type	EM	IN	YL	ST	Total
GRO01-Nutritional Intake Form	27	16	8	12	63

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17I

Breathing Outcomes - Status of enrollment and questionnaires by Center

CENTER		Follow-up	Consent	Baseline Completed[4]	6 month completed[4]	12 month	18 month	Died after
03	Case Western Univ	39	18	18	11	2	0	0
04	Univ. of Texas (D)	14	9	9	6	0	0	0
05	Wayne State Univ	4	0	0	0	0	0	0
08	Univ. of Miami	16	0	0	0	0	0	0
09	Emory University	16	6	2	0	0	0	0
11	Univ. of Cincinnati	15	4	4	3	1	0	0
12	Indiana Univ.	14	0	0	0	0	0	0
13	Yale University	3	1	1	1	0	0	0
14	Brown University	30	17	17	8	1	0	0
15	Stanford University	4	0	0	0	0	0	0
16	Univ. of Alabama	24	13	13	13	0	0	0
18	Univ. of Texas (H)	22	0	0	0	0	0	0
19	Duke University	11	0	0	0	0	0	0
20	Wake Forest	9	7	7	0	0	0	0
21	Children's (NY)	5	5	4	2	0	0	0
22	Univ. of Calif. At San Diego	35	9	9	7	2	0	0
Total		261	89	84	51	6	0	0

[1]Follow-up expected determined by SUPP09 Q1 Status[2]Consent granted determined by SUPF00 (Enrollment Log) [3] Consent granted Yes/No/Refused
[3]Discharge Baseline completed (SUPF01) determined by number of forms completed and transmitted to Data Center.
[4] 6 month completed (SUPF02) determined by number of forms completed and transmitted to Data Center.
[5] 12 month completed (SUPF02) determined by number of forms completed and transmitted to Data Center.
[6] 18 month completed (SUPF03) determined by number of forms completed and transmitted to Data Center. [7] Died after discharge determined by Interview Outcome

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.17J

SUPPORT Trial ROP Exam Tracking by Center

Center	# enrolled for the Center	# surviving to 31 weeks GA or 4 weeks of life (plus 4 week grace period)	# Examined at all	# final in both eyes	# final both eyes with Favorable Results	# final both eyes with Unfavorable Results	# final both eyes with Mixed Results	# final in only one eye	# non-final cases excused	# pending final status	# pending final status at least 50 wks PMA
03	40	39	23	21	15	6	0	0	0	18	1
04	15	14	9	8	7	1	0	0	0	6	1
05	4	4	0	0	0	0	0	0	0	4	0
08	17	17	17	1	1	0	0	1	0	16	16
09	22	20	16	5	2	3	0	0	0	15	6
11	20	16	11	8	6	2	0	0	0	8	7
12	16	14	9	7	6	1	0	1	0	7	2
13	3	3	1	0	0	0	0	0	0	3	1
14	33	31	24	17	16	1	0	0	0	14	3
15	4	4	2	2	2	0	0	0	0	2	0
16	40	30	27	21	20	1	0	0	0	9	7
18	26	23	16	6	5	1	0	0	0	17	9
19	16	12	10	1	0	1	0	0	0	11	11
20	9	9	9	6	6	0	0	0	0	3	3
21	8	6	5	4	2	2	0	0	0	2	0
22	43	35	33	21	17	3	1	1	1	13	12
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.
Generated from NG02, NG03, NG05, NF10, SUPP02, SUPP03, SUPP09, SUPP10

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.18A

Number of Forms in the Physiologic Definition Study - Status of Enrollment by Center

	Center	Screened	Eligible	Eligible with Consent	Enrolled	Challenged
03	Case Western	13	9	9	8	8
04	Texas - Dallas	107	34	34	15	15
05	Wayne State	0	0	0	0	0
08	Miami	120	4	4	3	0
09	Emory	20	5	5	1	1
11	Cincinnati	24	16	16	12	11
12	Indiana	35	9	9	7	7
13	Yale	15	7	7	4	4
14	Brown	40	19	19	16	16
15	Stanford	15	7	7	6	6
16	Alabama	16	3	3	1	1
18	Texas - Houston	8	3	3	1	1
19	Duke	6	1	1	1	1
20	Wake Forest	7	4	3	2	2
21	Rochester	5	0	0	0	0
22	UCSD	34	16	16	16	16
Total		465	137	136	93	89

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.18B

Number of Forms in the Physiologic Definition
By Form Type and Center

Form Type	CW	TX Dal.	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
PH01-Eligibility Form	13	103	113	17	21	34	15	40	12	15	8	4	7	5	29	436
PH02BASE-Oxy Reduct BL	6	15	.	1	10	7	4	16	6	1	1	1	2	.	16	86
PH02RA-Room Air Phase	6	15	.	1	9	6	3	16	4	.	1	1	1	.	16	79
PH2BSV02-Oxy Reduct BL	6	3	.	1	6	5	4	13	6	.	.	1	2	.	10	57
	31	**136**	**113**	**20**	**46**	**52**	**26**	**85**	**28**	**16**	**10**	**7**	**12**	**5**	**71**	**658**

(All Forms Completed between mm/dd/yy and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.19A

Number of Infants Enrolled in the Early Onset Sepsis Study
By Birth Month and Center

		Clinical Center																
	Birth Month	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	Total
RTI	May 2006	.	.	.	.	3	1	2	1	.	.	.	.	.	.	.	.	7
	Apr 2006	.	.	.	.	2	1	.	.	1	.	.	.	.	.	.	.	4
	Mar 2006	.	.	.	.	2	.	.	.	.	.	.	.	.	1	.	.	3
	Feb 2006	.	.	.	.	1	.	.	.	.	.	.	1	.	.	.	.	2
	Jun 2006	1	1	.	.	4	.	.	2	.	.	.	.	.	.	.	.	8
	Total	**1**	**1**	.	.	**12**	**2**	**2**	**3**	**1**	.	.	**1**	.	**1**	.	.	**24**

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 2.19B

Number of Forms in the Early Onset Sepsis Study
By Form Type and Center

Form Type	CW	TX Dal.	EM	CN	IN	YL	BR	TX Hstn.	WF	Total
EOS01-Screening Log	1	2	12	2	2	3	1	1	1	25
EOS02-Baseline	1	1	12	2	1	3	1	1	1	23
EOS03-Maternal Abx Form	.	2	10	.	.	3	1	1	2	19
EOS04-Infant Culture Form	1	1	12	2	1	3	1	1	1	23
EOS05-Infant Abx Form	1	1	12	2	1	3	1	1	1	23
EOS06-Clinical Evaluations/Outcomes	1	1	12	2	.	3	1	1	1	22
EOS07-Readmission	.	.	.	.	1	.	.	.	.	1
	5	**8**	**70**	**10**	**6**	**18**	**6**	**6**	**7**	**136**

(All Forms Completed between 01/01/98 and 06/30/06 - Table Produced on 07/11/06)
The date of form completion is generated by the data entry software.

CHAPTER THREE

Batch Edit

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 3.1

Summary of Batch Edits in the Previous Month
By Protocol and Center

			Clinical Center																
Batch Edit Status	Date	Protocol	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
Sent	06/06	AEEG	2	.	2	.	1	.	.	.	1	.	.	2	11	.	1	.	.	20
	06/06	Benchmarking Study	.	.	52	1	.	.	.	.	.	.	.	.	1	.	.	.	.	54
	06/06	CAND	.	.	1	1	2	16	2	1	.	6	22	3	39	1	.	.	.	94
	03/05	Cytokines Study	.	.	.	4	.	.	.	.	.	.	.	.	.	.	.	.	.	4
	06/06	Generic Database	4	2	122	16	3	46	4	2	.	4	.	21	26	3	4	1	13	271
	06/06	Generic Database Follow-up	3	2	10	11	6	18	12	3	1	4	1	6	30	.	.	4	82	193
	06/06	Glutamine Follow-up	.	.	.	4	2	.	2	.	.	.	.	.	.	.	.	.	.	8
	06/06	Glutamine Study	.	.	125	.	.	.	.	.	.	.	.	.	.	.	.	.	.	125
	06/06	Hypothermia Follow-up	.	.	.	.	.	3	.	.	.	.	.	2	7	.	.	.	.	12
	06/06	Hypothermia Study	.	.	87	.	.	.	.	.	.	.	.	1	9	.	.	.	.	97
	06/06	Phototherapy Study	.	.	19	2	.	.	.	.	.	.	.	.	4	.	.	.	.	25
	06/06	Preemie INO Study	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
	06/06	SUPP	5	.	.	3	.	.	.	.	.	.	5	.	22	.	.	10	.	45
			14	**4**	**418**	**42**	**14**	**83**	**20**	**6**	**2**	**14**	**28**	**35**	**149**	**4**	**5**	**15**	**95**	**948**
Unresolved	07/06	AEEG	2	.	2	.	1	.	.	.	1	.	.	1	11	.	1	.	.	19
	07/06	Benchmarking Study	.	.	52	1	.	.	.	.	.	.	.	.	1	.	.	.	.	54
	07/06	CAND	.	.	1	1	2	8	1	.	.	6	15	3	39	.	.	.	.	76
	04/05	Cytokines Study	.	.	.	4	.	.	.	.	.	.	.	.	.	.	.	.	.	4
	07/06	Generic Database	1	.	122	16	1	13	4	.	.	2	.	3	26	2	.	.	13	203

These reports only count errors such as range edit failures, skip pattern violations, and data inconsistencies.
First table is batch edits sent in the previous month.
Second table is unresolved batch edits in the previous month.
Other sites include TN and NM.

NICHD Neonatal Research Network

Monthly Report for the Period Ending 06/30/06

Table 3.1

Summary of Batch Edits in the Previous Month
By Protocol and Center

			Clinical Center																
Batch Edit Status	Date	Protocol	CW	TX Dal.	WS	MI	EM	CN	IN	YL	BR	ST	AL	TX Hstn.	DU	WF	NY	UCSD	OTHER	Total
	07/06	Generic Database Follow-up	1	2	10	5	6	3	9	2	1	2	.	1	30	.	.	1	82	155
	07/06	Glutamine Follow-up	.	.	.	4	2	.	2	.	.	.	.	.	.	.	.	.	.	8
	07/06	Glutamine Study	.	.	125	.	.	.	.	.	.	.	.	.	.	.	.	.	.	125
	07/06	Hypothermia Follow-up	.	.	.	.	.	.	.	.	.	.	.	2	7	.	.	.	.	9
	07/06	Hypothermia Study	.	.	87	.	.	.	.	.	.	.	.	1	9	.	.	.	.	97
	07/06	Phototherapy Study	.	.	19	2	.	.	.	.	.	.	.	.	4	.	.	.	.	25
	07/06	Preemie INO Study	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	0
	07/06	SUPP	5	.	.	3	.	.	.	.	.	.	5	.	22	.	.	10	.	45
			9	**2**	**418**	**36**	**12**	**24**	**16**	**2**	**2**	**10**	**20**	**11**	**149**	**2**	**1**	**11**	**95**	**820**

These reports only count errors such as range edit failures, skip pattern violations, and data inconsistencies.
First table is batch edits sent in the previous month.
Second table is unresolved batch edits in the previous month.
Other sites include TN and NM.

From: Zaterka-Baxter, Kristin
To: Chris Novak
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; mcollins@peds.uab.edu
Subject: RE: NICHD NRN Masimo Oximeters
Date: Wednesday, July 12, 2006 10:14:47 AM

Hi Chris,
If you can't locate the treatment assignments for the 10 Masimo oximeters UAB has, can you please send 10 more to UAB asap with treatment assignments sent only to me and we'll have UAB send the one with no assignments back to you.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Chris Novak [mailto:CNovak@masimo.com]
Sent: Tuesday, July 11, 2006 7:33 PM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Masimo Oximeters

Kris,
Unfortunately I have not been able to track down the assignment list, the procedure that we have in place to track this was not followed. I apologize for this delay but I will continue to look for the assignments and forward once it is retrieved.

Regards,
Chris

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, July 11, 2006 8:15 AM
To: Chris Novak
Subject: RE: NICHD NRN Masimo Oximeters

Chris,
Any luck in getting the treatment assignments for the masimo's sent to UAB as part of the Support trial?
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Chris Novak [mailto:CNovak@masimo.com]
Sent: Thursday, July 06, 2006 10:05 PM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Masimo Oximeters

Kris,
Sorry for the delay, but the person who programmed these is on vacation until Monday and has the serial number identification list. I have been unsuccessful at tracking them down but will try again tomorrow.

My apologies,
Chris

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, July 06, 2006 9:35 AM
To: Chris Novak
Subject: FW: NICHD NRN Masimo Oximeters

Hi Chris,
Please see below.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Wednesday, July 05, 2006 4:12 PM
To: 'MSayre@masimo.com'; 'VBishop@masimo.com'; 'CNovack@masimo.com'
Cc: Das, Abhik
Subject: NICHD NRN Masimo Oximeters

Hi all,
A gentle reminder to send a notification email with oximeter serial numbers and treatment assignments to me at RTI when shipping masimo study oximeters to the NICHD NRN research centers. The University of Alabama has received 10 oximeters and RTI as the DCC needs to give UAB the color codes that correspond to the treatment assignments for these instruments.

Below is a list of serial numbers for the oximeters received by UAB; please send me their respective treatment assignments (high/low).

328935
328981
329083
329168
329207
329689
329703
329706

329709
329713

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Tuesday, June 13, 2006 3:51 PM
To: 'MSayre@masimo.com'
Cc: Petrie, Carolyn; wrich@ucsd.edu
Subject: RE: SUPPORT

Hi Marybeth,
Please find attached a list of NRN coordinator/PI contacts; exiting centers and entering centers in 2006. Please make a note to send all masimo oximeter information (shipments with serial numbers and high/low assignments) to me prior to sending the actual shipments to any of the sites. I'll be keeping track for the data coordinating center. Please let me know if you have any questions.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Petrie, Carolyn
Sent: Sunday, June 11, 2006 10:52 PM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT

Kris-

Do you have a contact list that you could send her? I wasn't sure if I should send her the website information (just on the homepage). I am out of the office Mon and Tues attending a conference with Rose so will have limited access to email.

So nice to see you last week!
Carolyn

From: Wade [mailto:wrich@ucsd.edu]
Sent: Friday, June 09, 2006 6:33 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT

Carolyn,
Can you send this info to Maribeth at Masimo?
wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Friday, June 09, 2006 3:14 PM
To: Wade Rich (E-mail)
Subject: SUPPORT

Hi Wade,

Could you please send me a list of the centers that were dropped, and a list of the centers that were added?
If you have info about contact people at the new centers, that would also be useful.

Thanks,
Maribeth

From: Zaterka-Baxter, Kristin
To: mcollins@peds.uab.edu
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN Masimo Oximeters
Date: Wednesday, July 12, 2006 7:23:29 AM

Hi Monica,
The folks at Masimo still have not been able to locate the oximeter treatment assignments (email below). Hopefully this will be cleared up shortly but until then, please let me know if you think you will need more monitors in the next few days or over next week and we will find more to send you.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
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Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

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Kris,
Unfortunately I have not been able to track down the assignment list, the procedure that we have in place to track this was not followed. I apologize for this delay but I will continue to look for the assignments and forward once it is retrieved.

Regards,
Chris

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
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To: Chris Novak
Subject: RE: NICHD NRN Masimo Oximeters

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Any luck in getting the treatment assignments for the masimo's sent to UAB as part of the Support trial?
Thanks,
Kris

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kzaterka@rti.org

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Sent: Thursday, July 06, 2006 10:05 PM
To: Zaterka-Baxter, Kristin
Subject: RE: NICHD NRN Masimo Oximeters

Kris,
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Chris

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, July 06, 2006 9:35 AM
To: Chris Novak
Subject: FW: NICHD NRN Masimo Oximeters

Hi Chris,
Please see below.
Thanks,
Kris

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Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Wednesday, July 05, 2006 4:12 PM
To: 'MSayre@masimo.com'; 'VBishop@masimo.com'; 'CNovack@masimo.com'
Cc: Das, Abhik
Subject: NICHD NRN Masimo Oximeters

Hi all,
A gentle reminder to send a notification email with oximeter serial numbers and treatment assignments to me at RTI when shipping masimo study oximeters to the NICHD NRN research centers. The University of Alabama has received 10 oximeters and RTI as the DCC needs to give UAB the color codes that correspond to the treatment assignments for these instruments.

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Thanks,
Kris

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Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Tuesday, June 13, 2006 3:51 PM
To: 'MSayre@masimo.com'
Cc: Petrie, Carolyn; wrich@ucsd.edu
Subject: RE: SUPPORT

Hi Marybeth,
Please find attached a list of NRN coordinator/PI contacts; exiting centers and entering centers in 2006. Please make a note to send all masimo oximeter information (shipments with serial numbers and high/low assignments) to me prior to sending the actual shipments to any of the sites. I'll be keeping track for the data coordinating center. Please let me know if you have any questions.
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Petrie, Carolyn
Sent: Sunday, June 11, 2006 10:52 PM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT

Kris-

Do you have a contact list that you could send her? I wasn't sure if I should send her the website information (just on the homepage). I am out of the office Mon and Tues attending a conference with Rose so will have limited access to email.

So nice to see you last week!
Carolyn

From: Wade [mailto:wrich@ucsd.edu]
Sent: Friday, June 09, 2006 6:33 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT

Carolyn,
Can you send this info to Maribeth at Masimo?
wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Friday, June 09, 2006 3:14 PM
To: Wade Rich (E-mail)
Subject: SUPPORT

Hi Wade,

Could you please send me a list of the centers that were dropped, and a list of the centers that were added?
If you have info about contact people at the new centers, that would also be useful.

Thanks,
Maribeth

From:	Kathryn Fallon
To:	jon.e.tyson@uth.tmc.edu; woh@wihri.org; richard.ehrenkranz@yale.edu; sshankar@med.wayne.edu; dstevenson@stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; Wright, Linda (NIH/NICHD) [C]; skorones@utmem1.utmem.edu; edward.donovan@cchmc.org; Wally Carlo, M.D.; jlemons@iupui.edu; aaf2@po.cwru.edu; cbauer@peds.med.miami.edu; poo@rti.org; alaptook@wihri.org; barbara_stoll@oz.ped.emory.edu; arstark@bcm.tmc.edu
Cc:	Wally Carlo, M.D.
Subject:	FW:
Date:	Monday, July 10, 2006 5:20:26 PM
Attachments:	Fanaroff VLBW 1997 -2002 Revised 6July2006.doc

Dear Av:

Excellent draft and important message.

I have tracked changes.

A. My major concern is that the time periods compared vary, and it is not always clear which periods are being compared.

B. I would also emphasize the large decrease in mortality in <1.0 for 90-91 to 95 to 90.

C. New data should not be introduced in the discussion. Move to results.

I hope these comments are helpful.

Warmest regards,

Wally

REVISED: FEBRUARY 1ST 2006

TRENDS IN NEONATAL MORBIDITY AND MORTALITY FOR VERY LOW-BIRTH-WEIGHT (VLBW) INFANTS: FROM THE NICHD NEONATAL RESEARCH NETWORK

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Word Count: 2770 [minus abstract]

ABSTRACT

OBJECTIVE: To document the mortality and morbidity of infants weighing 501-1500 grams according to gestational age, birth weight, and gender.

STUDY DESIGN: Prospective collection of perinatal events and neonatal course to 120 days of life, discharge, or death from January 1990 through December 2002 at participating centers of the NICHD Neonatal Research Network on inborn infants.

RESULTS: ~~Compared~~ Survival improved substantially for 90-91 to 95-96, particularly for infants below 1000 gm compared with 1995-96. ~~survival~~ Survival for infants with birth weight between 501 and 1500 grams in 1997-2002,(84% to 85%) and survival without major neonatal morbidity [(including bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) or necrotizing enterocolitis (NEC)] remained static (70%). Multiple births (22% to 26%); antenatal corticosteroid utilization (71% to 79%); and maternal antibiotics (62% to 70%) increased~~.~~ ($p<.05$) from 1995-96 to 1997-2002. (How about ANS from 90-91 to 95-96?) -From 1997-2002, birth weight specific survival was 55% for 501 to 750 gm, 88% between 751 to 1000 gm, 94% for 1001 to 1250 gm, and 96% for infants 1251 to 1500 gm~~.~~ and ~~more females survived~~did not change when compared to 1995-96. (Or was this comparison within the 1997-2002 period?)

The incidence of NEC (7%), severe IVH (12%), and late onset septicemia (22%) remained essentially unchanged , but BPD slightly decreased from 23% to 22%. The use of postnatal corticosteroids declined from 20% in 1997-2000 to 12% in 2001-2002. (Is this the only comparison within the 97-02 period as in the abstract? You may want to be consistent and only use 95-96 vs 95-02 or 97-02 or 97-00 vs 01-02. Also, the latter compare 4 vs 2 years) Growth failure (weight <10th percentile) at 36 weeks' postmenstrual age decreased from 97% in 1995-1996 to 91% in 1997-2002 .

CONCLUSIONS: There ~~have been~~was a significant increase in survival but no significant increases in survival without neonatal and long-term morbidity among VLBW infants between ~~1997~~1991- to 2002 (?). We speculate ~~speculate~~ that to improve ~~improve~~ survival without morbidity requires determination, dissemination and application of best practice using currently available therapies plus identification of new strategies and interventions.

KEY WORDS: Very low birth weight, morbidity, mortality, NICHD Neonatal Research Network, prematurity, preterm delivery, limits of viability.

INTRODUCTION

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Advances in perinatal care that include antenatal corticosteroid therapy and postnatal surfactant administration ensure that most babies born before term in the USA now survive (1-6). Nonetheless, disorders relating to short gestation and low birth weight continue to contribute significantly to infant deaths in the United States (7-9). Indeed the infant mortality rate rose to 7.0/1000 live births in 2002 from 6.8 in 2001, marking the first increase in this rate in over four decades. Increases were distributed ~~fairly~~ widely across age, racial/ethnic groups, and geographic areas. The rise in infant mortality was attributed to increased births in both singleton and multiple deliveries with birth weight <750 g~~.~~m (to be consistent with style in abstract) (9) In addition, despite better predictors of preterm birth (10,11), efforts to reduce preterm births have failed, so that prematurity continues to contribute disproportionately to neonatal morbidity and subsequent physical and neurodevelopmental disabilities (12-15).

-__Determining the prognosis for survival, neuro-developmental outcome, and resource utilization of premature infants born at the threshold of viability (between 22 and 25 completed weeks of gestation) remains a major challenge and concern (16,17,18).

Our objective was to use the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Very-Low-Birth-Weight (VLBW) Registry to determine factors contributing to mortality and significant short-term morbidity among infants with birth weights between 501-1500 gm from 1997-2002. These outcomes were compared with our prior cohorts to document changes over the past twelve years and to examine the borders of viability.

METHODS

Study Population and Data Collection

This paper compares perinatal information, morbidities and mortality for three inborn cohorts of infants, all with birth weights between 501-1500 gm. Cohort I includes 1990-1991 births, the immediate post surfactant era. Cohort II, 1995-1996 births, reflects the sharp increase in antenatal corticosteroid use, and will be referred to as "1995/1996." Cohort III encompasses the time period from 1997-2002. It includes 18153 infants.~~comprises three epochs: the first includes 5885 infants born between 1/1/97 and 12/31/1998; the second comprises 5848 infants, born between 1/1/99 and 12/31/2000 and the third born between 1/1/2001 and 12/31/2002. Because no significant changes in outcome were observed between these time periods , this six-year period is considered as a single cohort referred to as "1997-2002".~~

All infants are part of the NICHD Neonatal Research Network VLBW Registry, wherein maternal and infant data were collected (with IRB approval) using common definitions developed by the investigators ~~(with IRB approval)~~ and described in the study *Manual of Operations* and in previous publications (1-5). Bronchopulmonary dysplasia (BPD), formerly called chronic lung disease (CLD), was defined by supplemental oxygen at 36 weeks' postmenstrual age as determined by the best obstetric estimate of gestational age at birth (19,20). In-hospital morbidity was defined by the presence of intraventricular hemorrhage (IVH) III-IV, necrotizing enterocolitis (NEC) (21) (I would limit to ≥2 and specify it here) and/or bronchopulmonary dysplasia (BPD) ~~(21,)~~, defined as on oxygen at 36 weeks. Mortality includes all deaths prior to 120 days of age. Intrauterine growth restriction and postnatal growth failure were defined by weight below the 10^{th} percentile according to the national reference data from Alexander (22). –Statistical comparisons between the different birth year cohorts were made by logistic regression for binary outcomes by adjusting for the birth weight and center unless indicated otherwise. The Cochran –Armitage trend test for contingency tables were used to test the overall trends in survival by birth weight and gestational age.

RESULTS

Survival and Morbidity

Mortality and selected morbidities among VLBW infants were compared for the three cohorts, "1990-1991", "1995/1996" and "1997-2002" for the same 12 centers participating in the Network throughout this time period. Mortality for the entire cohort declined from 20% in "1990-1991" to 16% (relative decline 20%, p<.0001) in "1995/1996", and 15% (relative decline 6%, p=0.9117) in "1997-2002". Most deaths occurred within 7 days of birth, and 87% of VLBW who died did so by 28 days. The change in mortality over time for each 250 gm birth weight category is evident in Figure 1. For the lowest birth weight group, 501-750 gm, mortality decreased from 59% in "1990-1991" to 46% in "1995/1996", a relative decline of 22% (p<.0001) and was 45% in "1997-2002", a further 4% improvement (p=0.6585). For infants whose birth weights were 751 to 1000 gm, mortality fell from 19% to 14% between "1990-1991" and "1995-1996", a relative decline of 21% (p<0.0001), and was 12% in "1997-2002" (a further 14% decline, p=0.3911). Among the 1001 to 1250 gm group, mortality fell from 7.7% in "1990-1991" to 6% in "1995/1996", a relative decline of 21% (p<.05), and was unchanged in "1997-2002". Among the heaviest group (1251 to 1500 gm), mortality decreased from 5% to 3%

between "1990-1991" and "1995/1996" (add the p value as in the others), was 4% in "1997-2002".

Figure 1 reveals that in-hospital morbidity, which includes IVH, NEC and BPD, according to birth weight increased between "1990-1991" and "1995/1996" (add the percentages and the p value), and was sustained at that level for "1997-2002". Combining the data for all birth weights, sSurvival with the various morbidities (BPD, severe IVH, NEC and all combinations thereof) increased slightly from 29% to 30% between "1995/1996" and "1997-2002" (p=0.0476), the exception being BPD alone which increased from 15% to 17% (p=0.0004). This translates into ~~a slight~~no improvement (71% vs. 70%) in the percentage of infants who survived without ~~significant neonatal~~in-hospital morbidity.

Perinatal parameters, for 1997-2002, are presented in Table 1. Because there was little change between 1997-1998 and 1999-2000, and 2001-2002, the combined numbers were used for comparison with previous reports. The center variability is obvious from the wide range of each parameter. Compared with "1995/1996", (reference 5) antenatal corticosteroid use increased from 71% to 79% (p<.0001) and maternal antibiotic administration increased from 62% to 70% (p<0.0001) (How about 90-91 data?). There has also been a 4% increase in multiple

births (p<.0001) and a 7% decrease in endotracheal intubation in the delivery room (p<.0001). Other parameters remained stable.

___The lower Caesarean section rates (49% versus 64%) and high rates of vaginal breech delivery (14% versus 4%) for ~~in~~ infants ~~with B.W>.of~~ 500-749 gm~~rams~~ compared with 751-1000 gm~~rams~~, (~~table1~~Table 1) suggests a less aggressive obstetrical approach for the most immature infants.

Selected morbidities, therapies, and mortalities for inborn infants are presented in Table 2. During "1997-2002" there was a reduction in RDS (44% compared with 50%, p<.0001), but more surfactant use (58% vs. 52%, p<.0001) than in "1995~~/~~-1996", and a similar number of PDA's that required treatment (29 % vs. 30%,) (Table 2). There were not much changes in other major morbidities including BPD, NEC, Grade III-IV IVH, PVL (5% vs 3%), late onset sepsis (24% vs 22%), and growth failure (97% vs 91%)~~.~~ (5,22,25). Postnatal corticosteroids were given to 12% of infants in 2001-2002 compared with 20% of all the infants in "1997-2000" and 23% in "1995/1996" (p<.0001). Survival data, with and without selected neonatal morbidities according to birth weight, are included in Table ~~2.3~~ 3.

Influence of Gender, Birth Weight and Gestational Age On Mortality

Separate logistic regression (23) models of mortality by birth weight and gestational age were developed for inborn singleton infants 4501-1500 gm~~rams~~ (verify it was done for 501, not 401) by gender for the 1997-2002 cohort. All models included birth weight, gestational age by best obstetric measures, and an interaction term between birth weight and gestational age. The plots are presented in Figure 2, for the cohort of infants >21 weeks and between the 5th and 95th percentiles of birth weight for each gender at each gestational age where a lower birth weight carried a higher mortality risk (22). Large reductions in mortality risk occur with each additional week of gestation and 100 gm increase in birth weight in the mid and lower gestational age and birth weight ranges. At higher gestational ages, comparable changes in birth weight have a smaller impact on mortality risk. Prediction of mortality risk at the lowest birth weights is influenced by gender (greater in males), and intrauterine growth rate. For both males and females, mortality risk contour lines generally traveled the graph from upper left to lower right, demonstrating a combined effect of gestational age and birth weight on risk of death. Hence, the mortality ranges from 60% for a 24 week female with a birth weight on the 5th percentile to 20% if they are on the 95th percentile; mortality for males of similar gestation ranges from almost 70% on the 5th percentile to 25% on the 95th percentile.

The birth weight specific survival for all inborn infants born between 1997 and 2002 is shown in Figure 3. Survival progressively rises with increasing birth weight. There is a striking stepwise increase in survival from 36% at 501-600g to 61% at 601-700g, and 79% at 801-900g. (A figure of survival by gestational age may be very useful as antenatally, weight measurements may not be as readily available.)

DISCUSSION

This report summarizes the mortality and morbidity among VLBW infants born at the 15 NICHD Neonatal Research Network Centers between 1997 and 2002. Comparison of outcomes throughout thirteen years is restricted to the 12 centers that participated throughout this time period. Between January 1997 and December 2002, 85% of inborn VLBW infants survived to discharge, ranging from 55% of infants who were 501-750 gm at birth to 96% for infants 1250-1500 gm at birth however there has been little change in survival by birth weight or gestational age categories during this time period.

Compared to "1990-1991", mortality rates fell significantly for VLBW infants, particularly for infants weighing less than 1000 gm at birth (Fig. 1). Respiratory distress syndrome remained the most common acute pulmonary disease, although there was a relative decrease of almost

20% in the frequency of the diagnosis when compared to the "1991" cohort (2,3).(Tese are new data. Only 95-96vs 1997-2002 were compared in results) The incidence of Grade III/-IV ~~intraventricular~~IVH hemorrhages declined from 15% in "1990-1991" to 12% in "1997-2002", but there has been no improvement since 1997.

Antenatal pharmacological therapies instituted in the face of impending preterm birth include steroids to induce maturity of fetal lungs and prevent brain hemorrhage; antibiotics to treat potential chorioamnionitis, prevent early onset Group B streptococcal (GBS) disease, and prolong the latent period; and tocolytics to extend the duration of pregnancy. The marked increase in antenatal steroid use from approximately 20% in "1990-1991" to 79% in "1997-2002" may, in part, explain the reduced mortality and lower incidence of RDS (3,5).

In "1990-1991" only 31% of women received antenatal and/or intrapartum antibiotics. This increased to 62% in "1995/1996" and reached 70% in "1997-2002". Early onset sepsis (EOS), proven by blood culture, declined from 19.3/1000 in 1991-93 to 15.4/1000 live births in 1998-2000 (25). Amongst VLBW infants GBS sepsis declined from 5.9/1000 in 1996 to 1.7/1000 births in 2000, but *Escherichia coli* (*E. coli*) sepsis increased from 3.2 to 6.8/1000 births with most *E. coli* isolates (85%) resistant to ampicillin. This reflects a worrisome change in the

pathogen distribution among VLBW with EOS (25), , perhaps a consequence of maternal antibiotic therapy. EOS remains an important risk for mortality; 37% of infants with EOS died compared to 13% without EOS.

~~Perinatal morbidity is significantly increased in multiple births: IVH, NEC, and/or BPD were more common in multiples than in singletons (p= 0.0010). The incidence of severe handicap is increased in survivors of multiple gestations (26).~~ Multiple births in the Network cohort now account for 26% of VLBW deliveries, compared with 19% in the early 1990's. Similar increases have been noted in the Vermont Oxford Network (6). An increasing number of multiple births are due to assisted reproductive techniques. In 1997, infants conceived with assisted reproductive technology accounted for 4.3% of very low birth weight infants (<1 kilogram) (26). Gestational age-adjusted comparisons of outcome between singletons and multiples have shown conflicting results.(27) Comparisons that corrected for relevant confounding variables show that twins and singletons have similar risks for early morbidity and mortality.(28) Second-born very low birth weight twins seem to be at risk for increased respiratory morbidity, even in the era of routine antenatal corticosteroids and postnatal surfactant therapy.and we observed that IVH, NEC, and/or BPD were more common in multiples than in singletons (p= 0.0010). The

incidence of severe handicap is increased in survivors of multiple gestations (26). ~~In addition to multiple births, elective emergent delivery for fetal compromise identified in extremely immature infants contributes to the continuing toll of preterm birth.~~

Postnatal steroid therapy has come under close scrutiny because of multiple complications that include adverse neurodevelopmental outcome, hypertension, hyperglycemia, sepsis, gastrointestinal perforations, and growth arrest, ~~and adverse neurodevelopmental outcome (27~~29-~~29~~31). Overall, the use of postnatal steroids declined from 19% in "1995/1996" ~~to~~ and 20% in "1997-2000", ~~and~~ to 12% in 2001-2002 (Mention 1990-91 data). This has been most notable for infants with a birth weight of 501-750 grams where the numbers have decreased from 53% in 1997-2000 to 30% in 2001-2002. . In response to the American Academy of Pediatrics' Committee of the Fetus and Newborn Statement, use of postnatal steroids should be carefully considered or should be discouraged and further declines should be anticipated.(~~30~~32)

Although survival rates improved, the incidence of major morbidities (including BPD, IVH and NEC) remains a serious concern. ~~The terms BPD (initially defined as oxygen at 28 days) and CLD (oxygen at 36 weeks' postmenstrual age) have been used interchangeably to refer to chronic lung disease (2-5). A consensus workshop has recommended the term BPD, because it~~

~~is clearly distinct from the multiple chronic lung diseases of later life (3133) and the use of a physiologic test confirming the necessity of supplemental oxygen at 36 weeks (3234).~~ BPD (oxygen at 36 weeks' postmenstrual age) increased from 19% in "1990-1991" to 23% in "1995/1996", and was 22% in "1997-2002". The improved survival rates of VLBW infants, particularly those weighing less than 1000 gm, may explain, in part, the consistent rate of BPD.

The mortality and morbidity for the smallest infants remain high with little change in survival by birth weight or gestational age on "1997-2002" compared with "1995-1996".

The female survival advantage extends through all birth weights and gestational ages as they behave as if they are a week more mature and 100 gm heavier than males (~~33~~35).

The mortality as well as the morbidity and outcome data are entirely consistent with those reported by the Vermont Oxford Network who also reported the plateau in mortality in the late 1990's. (6). There are dramatic stepwise increases in survival between 23 and 25 weeks' gestation and birth weights above 600 gm. Thus, from 23 to 24 completed weeks the survival increases from 29% to 60%, almost a 4% improvement in survival for each additional day *in utero*. The birth weight survival data are complementary as survival increases from 36% at 501-600 gm to 61% for a birth weight of 601-700 gm. Assuming an intrauterine weight gain of 15

gm/kg/day at this gestation, this also represents over 3% a day improvement in survival for each additional day *in utero*. The steep curve in survival continues between 24 and 25weeks' gestation and a birth weight of 701-800 gm. These data support the concept of extending the stay *in utero* until there is substantial evidence that the ELBW fetus is seriously compromised.

Viability, morbidity and resource use are the subject of much debate (~~30~~32). Both the American Academy of Pediatrics and the American College of Gynecologists have issued statements and guidelines concerning deliveries at the threshold of viability (25 or fewer completed weeks of gestation) (17, 18). They concur that it is extremely difficult for physicians and families to make decisions regarding the institution and continuation of life support in such infants.

If viability is defined by a survival rate of equal to or greater than 50%, our data imply that infants delivered at 24 weeks' gestation and with a birth weight of at least 600 gm are, indeed, viable. However, the definition does not take into account the considerable long-term neurodevelopmental deficits encountered at this weight and gestational age. In the ~~Epicure~~ EPICure Study, which included all infants born in the United Kingdom between 23 and 25 6/7 weeks' gestation, the mortality was high and less than half the survivors were neurologically

intact (14,15). Similar neuro-developmental outcomes have been reported from the USA (12,13). To gain perspective from the 1997-2002 cohort, approximately 40% of infants delivered at 24 weeks' gestation would die and 40% of the survivors manifest significant neurodevelopmental handicap; hence, only 36% could be anticipated to survive without major disability. Similar calculations from the 1995/1996 cohort at 24 weeks' gestation yield only 30% intact survivors. These are conservative and probably overly optimistic estimates as substantial visual integrative, mathematical and other learning problems are often identified in apparently neurologically intact, very low birth weight infants when they go to school (~~33~~35,~~34~~36). The long-term burden of extreme preterm birth may be even greater. There remains wide center variability in survival as well as the various short and long-term morbidities. The group data are robust but counseling individual pregnancies remains extraordinarily challenging and difficult. Furthermore, one can only speculate on the outcomes and costs, if all participating units were equally aggressive (or not) in their approach to infants at the boundaries of viability (15,34,~~35~~37,~~36~~38).

SUMMARY

Despite increased use of antenatal corticosteroids~~, antenatal antibiotics~~(delete antenatal antibiotics as they do not improve survival) and surfactant therapy, survival of VLBW infants changed almost imperceptibly between 1997-2002. There has been minimal change in the boundaries of viability and in the number of infants surviving without significant neonatal morbidity. Knowledge of birth weight, gestational age, gender, intrauterine growth rates, condition at birth, and site of delivery are needed to forecast the chances of an individual baby surviving. Long-term neurodevelopmental outcomes~~, still being evaluated for the most recent cohorts,~~ will ultimately determine the true outcome of this cohort of VLBW infants. Newer strategies and interventions are needed to prevent prematurity and improve the outcome of these vulnerable infants. The wide range of mortality and morbidities among Network centers suggests that there may be some "best practices" using currently available therapies that may be discoverable. Efforts are underway to find them.

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FIGURE LEGENDS

Figure 1. Comparison of mortality, morbidity and survival free from morbidity for very-low-birth-weight infants cared for in NICHD Neonatal Research Network Centers (n=12) in 1991, 1996 and 2000 by 250 gm birth weight intervals based on singleton infants born in those NICHD Neonatal Research Network Centers.

Figure 2. Mortality by birth weight, gestational age, and gender. The limits of the colored area indicate the upper 95th and lower 5th percentiles of birth weight for each gestational age. The curved lines indicate combinations of birth weight and gestational age with the same estimated probability of mortality, i.e., 10% to 90%. The gradation of color denotes the change in estimated probability of death: infants of lower gestational age and birth weight who are more likely to die are depicted in green; infants of higher gestational ages and birth weights who are less likely to die are portrayed in yellow.

Figure 3. Survival to discharge by birth weight in 100 gram increments among infants born in NICHD Neonatal Research Network Centers between 1/1/97 and 12/31/2002. ~~Data expressed as percentage survival for each birth-weight group for each two-year interval.~~

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TABLE 1

PERINATAL INFORMATION FOR INFANTS BORN IN THE NICHD NEONATAL RESEARCH NETWORK BETWEEN 1/1/97 AND 12/31/02[1]

Center ranges are represented in the parentheses

Birth Weight Group	501-750 g	751-1000 g	1001-1250 g	1251-1500 g	501-1500 g
N	4046	4266	4557	5284	18153
Birth weight					
Mean	635(611-652)	878(868-898)	1129(1110-1136)	1379(1370-1385)	1033(998-1066)
Standard deviation	69.1(64.9-72.2)	73.4(68.1-78.1)	71.5(68.9-75.7)	72.3(65.1-74.2)	289(273-295)
Antenatal steroids (%)	73(38-90)	84(50-94)	83(52-94)	78(47-89)	79(47-90)
Antenatal antibiotic	71(60-96)	70(62-88)	71(58-85)	69(55-87)	70(59-87)
Rupture of membrane > 24 hours*	26(17-35)	24(16-32)	24(18-29)	22(15-30)	24(16-28)
Multiple births	24(14-42)	24(14-36)	27(16-39)	29(17-44)	26(18-40)
Small for gestational age**	16(10-31)	15(9-22)	22(17-28)	28(16-35)	21(17-26)
Mode of delivery					
Vaginal vertex	38(12-46)	32(22-37)	35(26-46)	42(31-53)	37(29-44)
Vaginal breech	14(6-23)	4(<1-13)	2(0-5)	2(<1-4)	5(2-9)
Cesarean section	49(34-82)	64(57-74)	62(49-72)	56(45-68)	58(50-69)
Delivery room resuscitation					
Endotracheal intubation	78(57-98)	71(39-93)	46(18-69)	24(8-39)	53(32-68)
Resuscitation drug	10(<1-30)	6(<1-13)	4(<1-11)	3(0-8)	5(2-14)
Apgar score ≤ 3 at 1 min	54(36-69)	31(17-46)	21(11-33)	13(5-21)	28(18-39)
Apgar score ≤ 3 at 5 min	25(8-41)	7(3-15)	4(1-8)	2(<1-6)	9(5-12)

*Time between rupture of membrane and delivery.

** Small for gestational age as weight less than 10 th percentile.

[1] No significant difference was found between the epochs 1997-1998, 1999-2000.

TABLE 2
MORBIDITY AND MORTALITY FOR INFANTS BORN IN THE NICHD NEONATAL RESEARCH NETWORK BETWEEN 1/1/97 TO 12/31/02[1]
Center ranges are represented in the parentheses

Birth Weight Group	501-750 g	751-1000 g	1001-1250 g	1251-1500 g	501-1500 g
N	4046	4266	4557	5284	18153
Morbidity (%)					
Respiratory distress syndrome (RDS)*	71(51-98)	55(39-75)	37(22-65)	23(11-44)	44(30-69)
Surfactant theraphy	88(67-99)	74(50-93)	52(32-75)	32(17-52)	58(42-74)
Postnatal steroids	45(12-64)	25(7-46)	7(<1-16)	2(<1-4)	17(4-29)
Pneumothorax	13(1-19)	6(3-10)	3(0-6)	2(<1-4)	5(1-7)
Oxygen at 28 days	66(39-90)	37(15-70)	14(3-32)	5(<1-18)	25(11-41)
Broncho-pulmonary dysplasia (BPD)	46(25-81)	33(11-62)	14(3-46)	6(2-23)	22(10-50)
Patent ductus arteriosus (PDA)	49(20-83)	38(11-60)	23(9-48)	13(7-33)	29(13-50)
Indomethacin for PDA	84(62-98)	81(56-98)	75(47-96)	67(40-88)	79(53-91)
Surgery for PDA	29(8-53)	21(7-53)	10(2-30)	6(0-16)	19(8-35)
Growth failure^	97(92-100)	93(85-100)	87(74-96)	86(66-98)	91(83-98)
Discharged home on oxygen	28(<1-75)	18(1-53)	9(0-36)	4(0-23)	11(<1-37)
Sonogram done	96(91-100)	98(92-100)	95(57-100)	85(37-99)	93(67-100)
Grade I ICH	10(5-16)	11(5-22)	10(4-24)	11(5-29)	11(7-23)
Grade II ICH	7(2-15)	6(1-11)	4(0-16)	2(0-6)	4(<1-11)
Grade III ICH	12(3-19)	9(4-22)	6(1-9)	4(0-9)	7(3-11)
Grade IV ICH	12(9-21)	5(1-10)	3(0-5)	1(0-6)	5(3-8)
Preventricular Leukomalacia	4(0-10)	3(0-14)	2(0-5)	1(0-3)	3(1-5)
NEC (proven)	11(4-25)	9(3-18)	5(3-9)	3(1-8)	7(4-11)
Late onset septicemia	44(29-58)	30(16-46)	17(8-27)	7(1-15)	22(12-32)

* An infant was determined to have RDS if each of the following was true: required oxygen at 6 hours of life continuing to age 24 hours; demonstrated clinical features within age 24 hours; had need for respiratory support to age 24 hours; had an abnormal chest x-ray within age 24 hours.

^ Growth failure defined as weight <10th percentile at 36 weeks post-conceptual age.

[1] No significant difference was found between the epochs: 1997-1998, 1999-2000.

TABLE 3

SURVIVAL WITH SELECTED NEONATAL MORBIDITY FOR INFANTS BORN IN THE NICHD NEONATAL RESEARCH NETWORK BETWEEN 1/1/97 TO 12/31/02[1]

Center ranges are represented in the parentheses

Birth Weight Group	501-750 g	751-1000 g	1001-1250 g	1251-1500 g	501-1500 g
N	4046	4266	4557	5284	18153
Survivors (%)	55(38-76)	88(74-94)	94(91-97)	96(93-99)	85(79-93)
Survived with morbidity* (%)	65(48-80)	43(27-63)	22(10-33)	11(5-19)	30(21-43)
Survived with (%)					
BPD alone	42(15-61)	25(5-42)	11(1-21)	4(0-9)	17(4-26)
Severe ICH**	5(0-13)	6(2-17)	5(<1-8)	4(0-12)	5(2-10)
NEC alone	3(0-16)	3(1-13)	3(<1-8)	2(0-5)	3(<1-7)
BPD and Severe ICH	10(3-17)	4(2-11)	2(0-5)	<1(0-2)	3(1-6)
BPD and NEC	4(0-9)	3(0-6)	<1(0-2)	<1(0-2)	2(<1-3)
NEC and Severe ICH	<1(0-5)	<1(0-2)	<1(0-1)	<1(0-<1)	<1(0-1)
BPD and Severe ICH and NEC	1(0-3)	<1(0-3)	<1(0-<1)	<1(0-<1)	<1(0-<1)

* Morbidity defined as a diagnosis of broncho-pulmonary dysplasia (BPD), grade III-IV intracranial hemorrhage (ICH) or proven necrotizing enterocolitis (NEC).

** Severe ICH defined as grade III or IV. Grade III is defined if the ventricular size was enlarged; Grade IV is defined as blood/echodensity in the parenchyma.

[1] No significant difference was found between the two epochs: 1997-1998, 1999-2000.

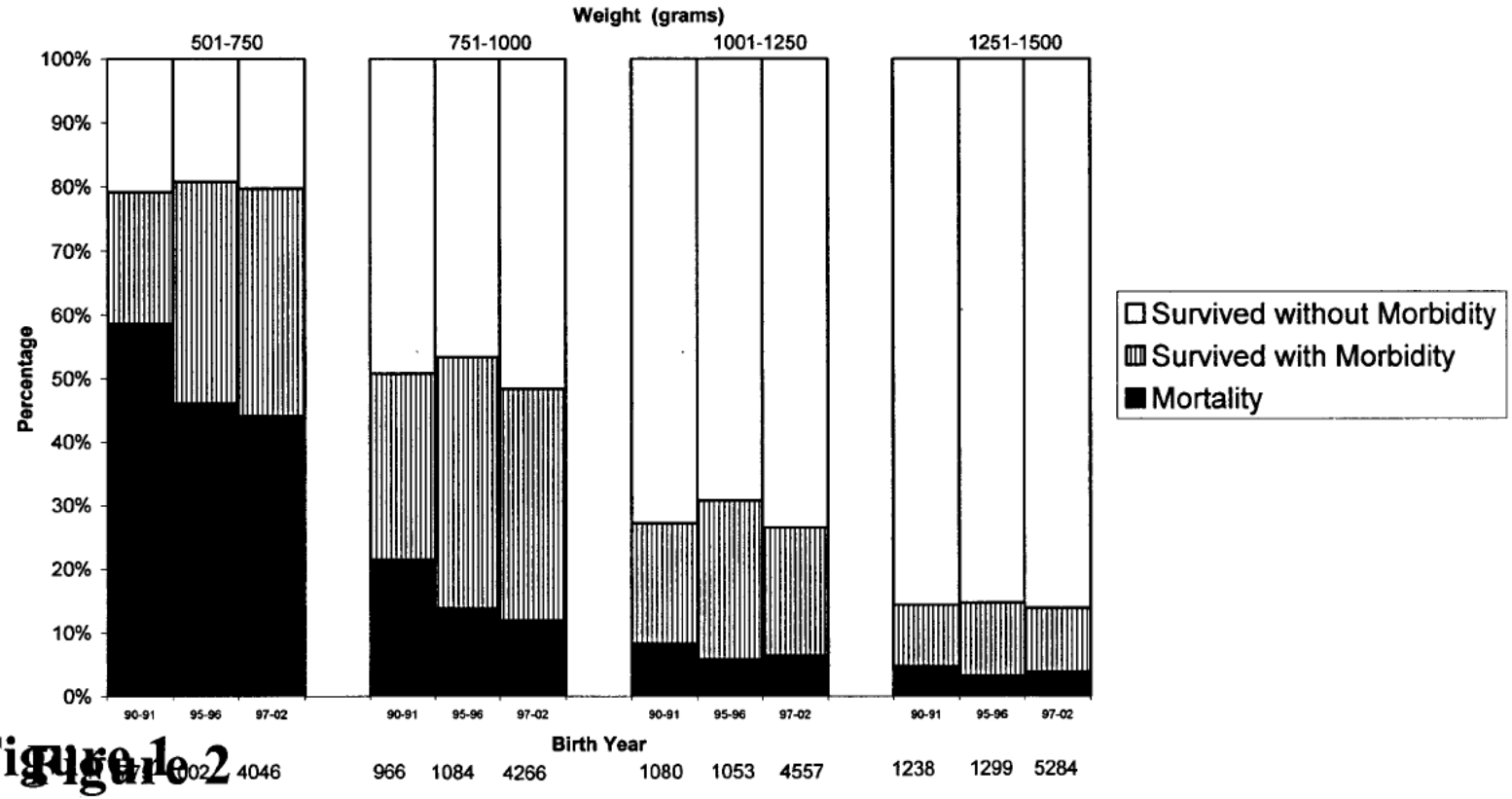


Figure 1

Figure 2

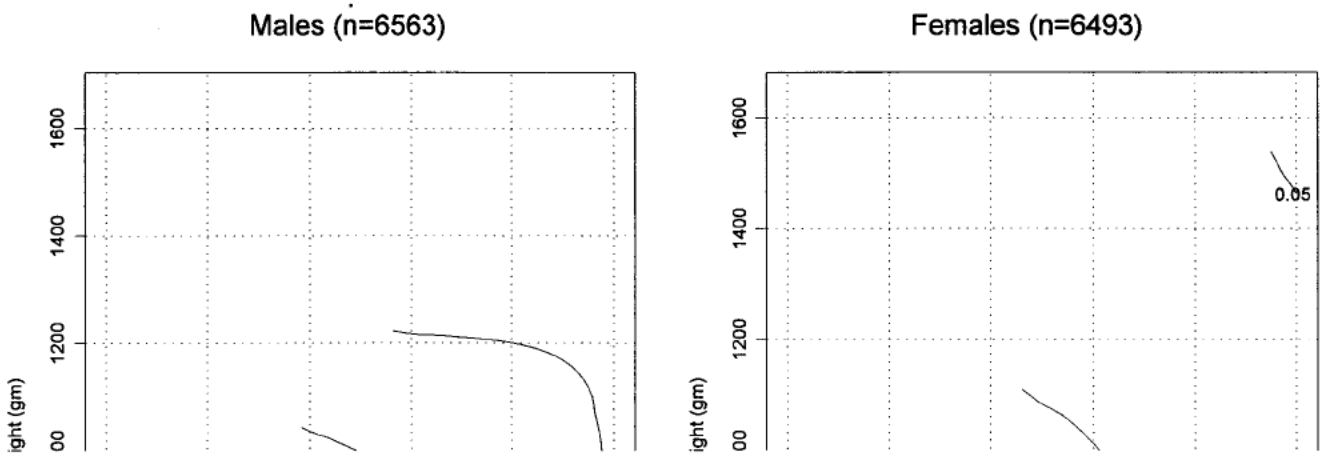
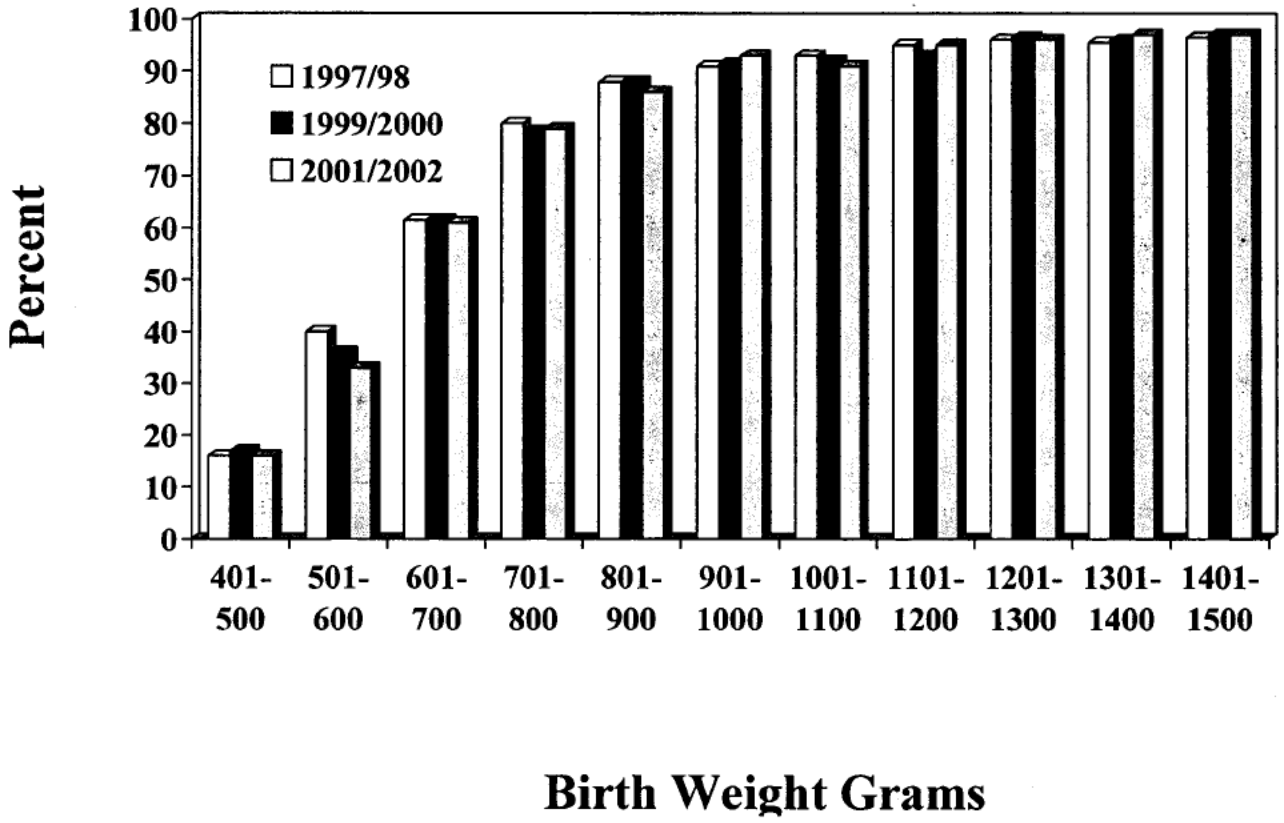


Figure 3 Survival by Birth Weight (%)



From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support enrollment
Date: Friday, July 07, 2006 1:00:29 PM

Total Support enrollment to date = 316
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Everett, Ruth; Neil Finer
Subject: RE: Masimo oximeters
Date: Friday, July 07, 2006 12:25:42 PM

Hi Rose,

I understand from Ruth that you would prefer to have us send out the modified oximeters to active SUPPORT sites and that Masimo will be sending us unaltered oximeters in exchange.

Good luck with enrollment.
Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, July 07, 2006 12:22 PM
To: Zaterka-Baxter, Kristin; Everett, Ruth; mcollins@peds.uab.edu
Cc: Das, Abhik; Gantz, Marie; Schaefer, Scott E.; Duara, Shahnaz; Neil Finer
Subject: RE: Masimo oximeters

Ruth
Thanks so much!!
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, July 07, 2006 11:17 AM
To: Reverett@med.miami.edu; mcollins@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Schaefer, Scott E.
Subject: Masimo oximeters

Hi Ruth,
Thanks so much for helping us out with the masimo shortage! Below is Monica Collins' home address for fed-ex Saturday delivery. Please send all 16 oximetes and docking stations 'priority overnight' to:

Monica Collins
(b) (6) [redacted]

Home phone: (205) 969-(b) (6) [redacted]

Below is the list of oximeter serial numbers we have for Miami for confirmation:

Serial Numbers	Color Codes
317217	ORANGE
317219	BLUE
317227	ORANGE
317312	BLUE
317363	BLUE
317384	ORANGE
317393	BLUE
317398	ORANGE
317399	ORANGE
317408	BLUE

317420	BLUE
317427	ORANGE
317431	BLUE
317438	ORANGE
317443	BLUE
317560	ORANGE

Thanks so much for everyone's help!
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Das, Abhik
To: Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: questions for SUPPORT neuro secondary
Date: Thursday, July 06, 2006 8:45:34 AM
Attachments: AbhikQuestions070506 (MG).doc

Susan:

I have had our programmers respond to your questions 1-3 (see attached), and Marie ran the numbers for the table. Of course, we don't have any eligibility numbers yet for the new sites that are coming on board. The projections of actual enrollment in SUPPORT were done using monthly average consent rates from our current data. One more comment I have related to #3 is that it would require significant additional programming work at our end. I am around today and tomorrow; so we can talk about your other data analysis ideas.

Thanks

Abhik

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, July 05, 2006 11:11 AM
To: Das, Abhik
Cc: higginsr@mail.nih.gov
Subject: questions for SUPPORT neuro secondary

Hi Abhik,

Please see attached. These are some "can we do it" questions for queries and edits, as well as some data requests for site-specific SUPPORT main trial eligibility #'s, projected enrollment. I am trying to put together an update, so I would really appreciate responses by the end of the week.

Thanks Abhik! Call me at 650-723(b) (6) if any of this is not self-explanatory. Will you be around on Thursday? I may call you to talk about this other data analysis idea re: highly advantaged vs. highly disadvantaged outcomes...

Thanks

Susan

Hi Abhik,

Jeanette Auman's comments are below in red.

The following questions are both general "can we do it" questions, and specific for the SUPPORT Neuroimaging secondary. I would really appreciate it if I could have responses by the end of the week. I am trying to put an update together. Please feel free to pass these questions/requests on to others – Thanks very much Abhik!!
****

1) Breaking up the MRI01 – As we discussed, breaking up MRI01 so that Part A completion is required within 2 weeks for every patient enrolled in SUPPORT from every site that is enrolling in the Neuroimaging secondary (that means all sites except Emory, Yale, Cincinnati). My questions about this are:

a) How does this sort of thing usually work? That is, will there be a prompt of some kind for the data entry/coordinator folks, or are they just supposed to know (from previous instructions) to go to MRI01 and complete Part A within 2 weeks of enrollment? I understand that RTI can they send a query to the site after 2 weeks if this is NOT done, I just want to get a handle on how it will all work –

I believe it should initially be discussed on the coordinators call, so that everyone is clear when this form is expected. Then the centers will receive a "missing forms" report stating that at least Part A of the MRI01 is expected within 2 weeks of the patient's enrollment into the Support protocol for all patients who have an SUPP02 form with Q. D1 = 'Y'.

The staff will then key the information in Part A of the MRI01, if the response to Q. A1 = 'N', the sites should be able to complete the form immediately. If not, Q. A1 = 'Y', then they will leave the form "incomplete" in the data entry system until they have the additional information to key.

2) Completion of MRI01 – We will also need a query for completion of the rest of MRI01 for all patients for whom the answer to MRI01 part A was "yes". But as I look at the form for the ten millionth time, I realize that I just constructed the early cranial US question (Part B) to ask WHEN the early US was done. I did not ask specifically whether or not the patient HAD an early cranial US and if not, why not. So, here are my questions:

a) Is there some way to "retrofit" that question (Part B)? Can the folks entering the data at the sites put stars where the month/day/year answer is for Part B.1, and enter a comment?

The sites can currently key missing codes into the date field and then create a comment stating that the US was not done. They will also be required by the DMS to key a missing code for Q. B2, but the remainder of section B would not be required.

I believe the form could also be updated adding a gate question to Section B, "Was an early cranial US done?" Y/N. Providing the directions, "if 'Y', complete the remaining questions in the section". We could update it in the data entry system once the process of upgrading all the computers at the sites is complete.

b) Can we have a query/edit generated for COMPLETION of the MRI01 form at discharge or status for all patients for whom MRI01 Part A was = enrolled? I would think a 2-week grace period would be enough, but I would be very happy to have your suggestion on timing –

All forms that are keyed into the data are required to be flagged complete in the data management system at some specified time point, regardless of the answer to specific questions on the form. Once flagged "Complete" the end of record check runs on the form data to determine whether or not it is completed as expected. For example, if Q. A1 is 'N', Q. A1a is expected, otherwise, Q. B1, B1a, C1 are expected. If Q. C1 is 'N', Q. C1a is expected, etc. Then the data will be again edited here at RTI once a month.

For the MRI01 form, the batch edits report will produce a failure if it is not marked complete by the time of the patient's status + 1 month, regardless of the value to Q. A1. The 1 month grace period is a typical grace period added to specific time points to allow sites to key their data, but we can make it 2 weeks if you are more comfortable with that.

3) Queries to sites for receiving MRI and CUS at RTI –

a) Can we have a query generated if CUS and MRI are NOT RECEIVED at RTI? I suppose this query would have to be a bit more complex - that is, cross-checked against the MRI01 answers and queries on the neuroimaging studies that were actually done. I would think that a 4-week grace period for this query would be OK, but again I would love to have your suggestion on timing –

This would require RTI staff to key the information of receipt of the imaging studies into a compatible data entry system, either an excel file or an Access data entry system, then we can programmatically send a query to the sites comparing the MRI01 data to the CUS and MRI not received at RTI. A month grace period seems reasonable.

4) The final question I have (for now) is a bit more involved. I would like to have some estimates on enrollment for the sites participating in the Neuroimaging secondary so I can number crunch. I realize that we do not have hard number for the 4 new sites, but I am sure there are some projected numbers floating around RTI. **The following mock table should be pretty self-explanatory – if not, let me know:**

Updated projected enrollment for SUPPORT and SUPPORT Neuroimaging Secondary

NETWORK SITE	**# patients/year ELIGIBLE for SUPPORT main trial (2005 #s or projected for new sites)**	**# patients/year PROJECTED to actually enroll in SUPPORT**	**Embedded or separate consent for SUPPORT Neuroimaging secondary**	**Projected annual enrollment in SUPPORT Neuroimaging**
Alabama	107	59	Not answered	I will do this
Case	64	44	Separate	I will do this
Dallas	46	36	Separate	I will do this
Wayne	16	16	Separate	I will do this
Indiana	43	27	Separate	I will do this
Brown	46	30	Separate	I will do this
Stanford	24	16	Embedded	I will do this
Houston	49	28	Embedded	I will do this
Duke	46	26	Separate	I will do this
Iowa			Embedded	I will do this
New Mexico			UNKNOWN	I will do this
Utah			Embedded	I will do this
Boston			Embedded	I will do this
TOTAL	441	282		I will do this

From: Gaynelle Hensley
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT MRI
Date: Wednesday, July 05, 2006 4:30:57 PM

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
06/29/06 2:09 PM >>>
Your site has indicated that IRB approval has been granted for the SUPPORT Neuroimaging secondary.

Please respond to the following questions by July 5th:

How many patients have been enrolled in the Neuroimaging secondary at your site?
1 patient has consented.

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?
No, Our 1st patient is scheduled for 7/706

Also, as a reminder, we are asking that study-related MRI's and cranial US be sent to RTI routinely - the manual indicates that neuroimaging CD's should be sent to RTI monthly, although this may not be necessary for all sites depending on the volume of enrollment. The reason we have requested that neuroimaging be sent routinely is two-fold: 1) this procedure will facilitate "rolling" central reading, particularly of the MRI's, and 2) it is likely to be easier for sites to obtain CD duplicates of studies soon after they are completed rather than at the end of the trial.

Below is the section of the manual pertaining to preparing and sending neuroimaging studies.

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 (Digital Imaging and Communications in Medicine) viewer); an example of this type of software is ShowCase(r) by Trillium.
There are many different viewer programs, but radiology departments are
quite familiar with them.

Removing PHI from digitized images may be difficult for some
centers. Radiology departments at most centers can create duplicate "anonymous exams" on their systems; these "anonymous exams" may then be
copied to CD. This procedure, which removes PHI from the image headers,
has been particularly useful in previous MRI-related research. Radiology
departments at other centers may use software that allows for alteration
or "blacking out" of PHI headers after images are transferred to CD. However, if these options are not available at your center, additional language could be added to the secondary consent form explaining that central readers will interpret the images, which include headers, but will not have other information about the patient. Each center will need
to work with their individual Radiology departments, and follow the requirements of their IRB with respect to the consent process.

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.

Kristin Zaterka-Baxter

4426 South Miami Blvd.

Durham, NC 27703

919-485-7750

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: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org; sduara@miami.edu
Subject: SUPPORT growth study
Date: Wednesday, July 05, 2006 3:32:40 PM

Rose,

I have a few questions about the growth secondary for SUPPORT.

1. The growth data (GRO-1) needs to be collected at 36 weeks and /or discharge, not both. I thought it was whichever time point came first.
2. For infants who are in the 27 week range at birth, their 32 week info may come just a few days past the 28 day info. Why are we collecting 32 week info? If a baby's dates for 28 days and 32 weeks adjusted age are in the same week, can we use the same data?

Thanks,
Ellen

From: Neil Finer
To: Michele Walsh; Wally Carlo, M.D.; petrie@rti.org; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; poo@rti.org; nxs5@cwru.edu; Wade Rich; mgantz@rti.org
Cc: kzaterka@rti.org; cdg2749@yahoo.com; Marsha Sumner; Fernando Martinez; bvecchio@careNE.org; rwebb@rti.org
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Wednesday, July 05, 2006 11:35:14 AM

HI Michele
This is well stated and I agree.
Talk to you next week.
I will review the manuscript and get back to you
Neil

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Wednesday, July 05, 2006 7:07 AM
To: Wally Carlo, M.D.; Neil Finer; petrie@rti.org; Bradley.Yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; higginsr@mail.nih.gov; adas@rti.org; poo@rti.org; nxs5@cwru.edu; Wade Rich; mgantz@rti.org
Cc: kzaterka@rti.org; (b) (6) ; Marsha Sumner; Fernando Martinez; bvecchio@careNE.org; rwebb@rti.org
Subject: Re: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Colleagues:
I would suggest that we all learn from the Bench trial.
It is not clear how CPAP might decrease BPD (or for that matter the evidence that it does decrease BPD is of a relatively low quality.) This trial attempts to provide that evidence.
Our analyses are by intent to treat. I suggest we look at the intent to provide the CPAP intervention vs the intent to provide surfactant and ventilation; looking at the protocol violations is the best measure of this intent. I think that we should NOT look at any other measure of separation. Regarding possible harm from a DR intervention: I am reassured that in the combined data that adverse events, particularly CPR and severe IVH, are lower than the mean rates in the network pre trial. Beyond that, we must trust the DSMC (and RTI) to monitor differences between the groups.
Regards, Michele

> ----- Original Message -----
> **From:** Wally Carlo, M.D.
> **To:** nfiner@ucsd.edu ; petrie@rti.org ; mcw3@case.edu ; Bradley.Yoder@hsc.utah.edu ; Roger.Faix@hsc.utah.edu ; alaptook@WIHRI.org ; kurt.schibler@cchmc.org ; higginsr@mail.nih.gov ; adas@rti.org ; poo@rti.org ; nxs5@cwru.edu ; wrich@ucsd.edu ; mgantz@rti.org
> **Cc:** kzaterka@rti.org ; cdg2749@yahoo.com ; Marsha Sumner ; fmartinez@ucsd.edu ; bvecchio@careNE.org ; rwebb@rti.org
> **Sent:** Saturday, July 01, 2006 9:14 PM
> **Subject:** Re: SUPPORT conference call, Mon Jun 19, 12-1pm ET
>
> I think # of days alive off the bent during the first 14 days (the duration of the intervention). May be the best. If there is no separation, there are many steps we could take.
> Wally
>
> -----Original Message-----
> From: Neil Finer <nfiner@ucsd.edu>
> To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Petrie, Carolyn <petrie@rti.org>; Michele Walsh <mcw3@case.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; Roger Faix <Roger.Faix@hsc.utah.edu>;

alaptook@WIHRI.org <alaptook@WIHRI.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Das, Abhik <adas@rti.org>; Poole, W. Kenneth <poo@rti.org>; nxs5@cwru.edu <nxs5@cwru.edu>; Wade Rich <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>
CC: Zaterka-Baxter, Kristin <kzaterka@rti.org>; cdg2749@yahoo.com <cdg2749@yahoo.com>; Marsha Sumner <MSumner@peds.uab.edu>; Fernando Martinez <fmartinez@ucsd.edu>; bvecchio@careNE.org <bvecchio@careNE.org>; Webb, Robin E. <rwebb@rti.org>; Wade Rich <wrich@ucsd.edu>
Sent: Sat Jul 01 19:58:06 2006
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hi Wally

I am worried about suggesting that the DSMC define adequate separation in the Vent/CPAP arm as we have not pre-specified any degree of such separation. What would they look at – days of ventilation? Could this lead to a concern of lack of separation, and a consideration for stopping? Do we know what minimal separation would be required to improve the occurrence of survival without BPD etc? There is current information that suggests that early ventilation within the first 3 days of life increases the risk of BPD/CLD, and that the duration of ventilation is directly related to the BPD/CLD risk. Unless this is a safety issue, I would not want to encourage such a look. Our safety outcomes include air leaks and IVH.

I would ask that we consider this important issue raise by Wally and perhaps have this discussed at the Steering Committee. I will join by conference call for that meeting.

Please share any thoughts on this issue with everyone and let's decide how to move ahead.

If necessary we can have a teleconference next week before the Steering Committee meeting.

Be well

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Saturday, July 01, 2006 1:36 PM
To: Neil Finer; Petrie, Carolyn; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin (b) (6) ; Marsha Sumner; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil:

We also discussed that RTI and the DMC should also do some process/measures evaluation to make sure the CPAP/ventilation arms are being separated enough by appropriate compliance with the protocol.

I like Michele's ideas about compliance.

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

Phone: (205) 934 4680

FAX: (205) 934 3100

Email: wcarlo@peds.uab.edu

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, June 27, 2006 5:11 PM
To: Petrie, Carolyn; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin(b) (6) Marsha Sumner; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone

Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.

Regards

Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin(b) (6); msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Reminder for Monday's call

The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19

12:00-1:00pm ET

To join the call,

Dial Toll Free, 866-675(b) (6)

Passcode: (b) (6)

Agenda

Trial Progress

New Site Orientation

Recruitment

SUPP05 Form - Newman

New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From: Susan Hintz
To: adas@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: questions for SUPPORT neuro secondary
Date: Wednesday, July 05, 2006 11:11:29 AM
Attachments: AbhikQuestions070506.doc

Hi Abhik,

Please see attached. These are some "can we do it" questions for queries and edits, as well as some data requests for site-specific SUPPORT main trial eligibility #'s, projected enrollment. I am trying to put together an update, so I would really appreciate responses by the end of the week.

Thanks Abhik! Call me at 650-723-(b) (6) if any of this is not self-explanatory. Will you be around on Thursday? I may call you to talk about this other data analysis idea re: highly advantaged vs. highly disadvantaged outcomes...

Thanks

Susan

Hi Abhik,

The following questions are both general "can we do it" questions, and specific for the SUPPORT Neuroimaging secondary. I would really appreciate it if I could have responses by the end of the week. I am trying to put an update together. Please feel free to pass these questions/requests on to others – Thanks very much Abhik!!
****

1) Breaking up the MRI01 – As we discussed, breaking up MRI01 so that Part A completion is required within 2 weeks for every patient enrolled in SUPPORT from every site that is enrolling in the Neuroimaging secondary (that means all sites except Emory, Yale, Cincinnati). My questions about this are:

a) How does this sort of thing usually work? That is, will there be a prompt of some kind for the data entry/coordinator folks, or are they just supposed to know (from previous instructions) to go to MRI01 and complete Part A within 2 weeks of enrollment? I understand that RTI can they send a query to the site after 2 weeks if this is NOT done, I just want to get a handle on how it will all work –

2) Completion of MRI01 – We will also need a query for completion of the rest of MRI01 for all patients for whom the answer to MRI01 part A was "yes". But as I look at the form for the ten millionth time, I realize that I just constructed the early cranial US question (Part B) to ask WHEN the early US was done. I did not ask specifically whether or not the patient HAD an early cranial US and if not, why not. So, here are my questions:

a) Is there some way to "retrofit" that question (Part B)? Can the folks entering the data at the sites put stars where the month/day/year answer is for Part B.1, and enter a comment?

b) Can we have a query/edit generated for COMPLETION of the MRI01 form at discharge or status for all patients for whom MRI01 Part A was = enrolled? I would think a 2-week grace period would be enough, but I would be very happy to have your suggestion on timing –

3) Queries to sites for receiving MRI and CUS at RTI –

a) Can we have a query generated if CUS and MRI are NOT RECEIVED at RTI? I suppose this query would have to be a bit more complex - that is, cross-checked against the MRI01 answers and queries on the neuroimaging studies that were actually done. I would think that a 4-week grace period for this query would be OK, but again I would love to have your suggestion on timing –

4) The final question I have (for now) is a bit more involved. I would like to have some estimates on enrollment for the sites participating in the Neuroimaging secondary so I can number crunch. I realize that we do not have hard number for the 4 new sites, but I am sure there are some projected numbers floating around RTI. **The following mock table should be pretty self-explanatory – if not, let me know:**

Updated projected enrollment for SUPPORT and SUPPORT Neuroimaging Secondary

NETWORK SITE	**# patients/year ELIGIBLE for SUPPORT main trial (2005 #s or projected for new sites)**	**# patients/year PROJECTED to actually enroll in SUPPORT**	**Embedded or separate consent for SUPPORT Neuroimaging secondary**	**Projected annual enrollment in SUPPORT Neuroimaging**
Alabama			Not answered	I will do this
Case			Separate	I will do this
Dallas			Separate	I will do this
Wayne			Separate	I will do this
Indiana			Separate	I will do this
Brown			Separate	I will do this
Stanford			Embedded	I will do this
Houston			Embedded	I will do this
Duke			Separate	I will do this
Iowa			Embedded	I will do this
New Mexico			UNKNOWN	I will do this
Utah			Embedded	I will do this
Boston			Embedded	I will do this
TOTAL				I will do this

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Agenda for the SUPPORT Trial Subcommittee Meeting
Date: Wednesday, July 05, 2006 10:35:59 AM

Rose:

I personally think we have discussed #5 ad nauseum, and it is really a bigger issue than just the SUPPORT trial. However, I understand if you were thinking about a narrower discussion of the statement that Neil has crafted on this issue.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, July 05, 2006 10:32 AM
To: Neil Finer; Wally Carlo, M.D.; Michele Walsh; Bradley Yoder; Roger Faix; Abbot Laptook; kurt.schibler@cchmc.org; Das, Abhik; Nancy Newman; Gantz, Marie; Poole, W. Kenneth
Cc: Petrie, Carolyn; Zaterka-Baxter, Kristin
Subject: Agenda for the SUPPORT Trial Subcommittee Meeting

HI,
Attached is the agenda for the SUPPORT Subcommittee. Please send comments on the agenda items (additions, etc.) to the group.
Thanks
Rose
<<Agenda for the SUPPORT Trial Subcommittee Meeting.doc>>

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Das, Abhik
Subject: FW: Fi02% adjustment for altitude
Date: Wednesday, July 05, 2006 7:19:26 AM

Hi,
Just FYI.

Please see the response below from Dr. Faix re. infants in 02 at 36 weeks.
Thanks,
Kris

-----Original Message-----
From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Monday, July 03, 2006 6:45 PM
To: Zaterka-Baxter, Kristin
Subject: Re: Fi02% adjustment for altitude

Out of 350 or so kids <1500 gm BW per year, our rough guesstimate would be that 50-60% are still on supllemental oxygen at 36 weeks corrected GA.

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 6/22/2006 2:12 PM >>>
Hi,

Would it be possible to estimate what percent of infants are on oxygen at 36 weeks in your Centers?

Thanks,

Kris

Kris Zaterka-Baxter

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (191) 485-7762

kzaterka@rti.org

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 22, 2006 7:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: Neil Finer; Das, Abhik; Petrie, Carolyn; Fernando Martinez; Wade Rich
Subject: Fi02% adjustment for altitude

Hi,

For the Support study, Dr Yoder (Utah) has suggested the following adjustment in Fi02% to determine what is considered in room air at high
altitudes (5000 feet) based on barometric pressure. This will affect Utah and NM. Below is the suggested adjustment:

"Adjust all the FiO2 variables by a factor of 1.22 to account for the altitude at SLC compared to the other centers. Thus, "21%" at sea level
is equivalent to 21*1.22 or 25.6% at 5000 feet. For ease of use we will assume that infants in < 25% FiO2 would be in room air at sea level."

Thanks,

Kris

From: Neil Finer
To: Susan Hintz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: adding a question to SUPPORT forms?
Date: Sunday, July 02, 2006 6:46:32 PM

Thanks Susan
I think that I will have some further discussion with these sites.
I want your study to be a success and we need every baby to be evaluated.
I will let you know what I can learn
Be well
Neil

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, June 30, 2006 7:53 AM
To: Wade Rich
Cc: Neil Finer
Subject: RE: adding a question to SUPPORT forms?

Neil and Wade:

I have been trying to keep a running spreadsheet with approvals, dates, reasons for delays or non-participation. Here is what I have about reasons:

1) Yale: Per 3/24 email from Richard Ehrenkranz - Not participating due to "possible need for sedation for MRIs" - particularly an issue with their IRB. I also gather there was disagreement about whether MRI would really add anything - perception that it is not worth the trouble.

2) Cincinnati: Per 3/31 email from Estelle Fischer to Kris Zaterka, reasons for not participating are: 1) doubt over "quality of images at 35-42 wk", 2) sedation would not be allowed by IRB, 3) "safety" - i.e., neonatology attending would be responsible for safety of patient in the MRI suite and since this is a "study protocol" it wouldn't be worth the perceived risk, 4) research slots for MRI are limited

3) Emory: I see I don't have the reason on my spreadsheet, but I know I have it in an email somewhere from Ellen Hale, so I will get back to you.

Wade - I was also surprised that Boston would participate. But, in fact they have reported that they intend to enroll with an embedded consent - their IRB will review on 7/11. Iowa and Utah also will be enrolling with an embedded consent. Both those sites have provisional approval from their IRBs with minor modifications. I have sent another round of emails through Rose to get a response from New Mexico about their participation - we have not yet heard from them. Do you know where they stand in terms of SUPPORT main trial?

Neil - Abhik will begin working with the programmers to break up the MRI01 and include automatic
queries to sites with Neuroimaging secondary approval for all patients enrolled in SUPPORT if RTI MRI01 info not received within 2 weeks. I am now aware of at least 6 additional patients enrolled in the Neuroimaging seccondary, but the MRI01 forms were apparently not keyed or lost in cyberspace. Hopefully these changes will make everything better.

Thanks

Susan

Probably won't get Boston either, as I believe they transfer their kids before 36 wks to a non-MRI facility.

wade

From: Neil Finer
Sent: Thursday, June 29, 2006 5:34 PM
To: Susan Hintz
Cc: adas@rti.org; higginsr@mail.nih.gov; Wade Rich
Subject: RE: adding a question to SUPPORT forms?

Susan

Why will these sites not be enrolling? Cost, availability, competing studies?

Thanks

Neil

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Thursday, June 29, 2006 8:25 AM
To: Neil Finer
Cc: adas@rti.org; higginsr@mail.nih.gov
Subject: RE: adding a question to SUPPORT forms?

Thanks Neil. As you know, the MRI01 was formulated in part to be the "study log" for this secondary. However, I am uncovering some issues and problems; for one, it appears that the MRI01 is not being completed and keyed routinely whether or not a patient has been enrolled in the secondary. I am aware of several patients that HAVE been enrolled in the secondary, but it is not reflected in the monthly report presumably because the MRI01 was not completed by the site. I think this can be easily remedied. I will take your advice with respect to not adding a question to the main SUPPORT data collection instruments. I will work with RTI to break up the MRI01 questions (as I mentioned previously, part A of the MRI01 is essentially a study log query), and I have also asked that missing form requests be routinely sent for the MRI01 to all sites with IRB approval for the secondary for all patients enrolled in SUPPORT main trial. Once we have the MRI01 "break up" dealt with, we will also reiterate the requirement of answering the study log query from the MRI01 for ALL PATIENTS ENROLLED IN THE SUPPORT TRIAL (not just patients enrolled in the secondary).

To update you, the following sites have definitively indicated they will NOT be participating in the neuroimaging secondary:

Emory

Yale

Cincinnati

Thanks again,

Susan

Hello Susan

I have discusses this and given it a lot of thought. I believe that the MRI secondary should have its own Study Log. This is the case for all
other studies including the Breathing Outcomes Secondary.
All eligibles are entered, and when consented that is indicated. This then becomes part of the monthly report, and all sites are already familiar with this concept, and this is consistent with Network practice.
Perhaps describing the problems that Stanford and other centers have had
in enrolling infants in the MRI secondary would be helpful. To my knowledge, we are the only center that has actually enrolled in this Secondary and completed the MRs.
Hope this helps
Neil
-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, June 28, 2006 10:07 AM
To: Neil Finer
Subject: adding a question to SUPPORT forms?

Hi Neil,

I continue to track the sites regarding their involvement in the SUPPORT Neuroimaging secondary. There is still a great deal of foot-dragging, and I am getting ready to send out another round of emails. However, to properly track involvement/enrollment in the secondary and be able to follow-up with the sites on an individual patient basis, I think it is necessary to add a question querying whether the patient has been consented for the Neuroimaging secondary
to the main trial data collection instruments. In my attempt to limit additional data collection and make things "easy" for the folks enrolling in the Neuroimaging secondary, I constructed the MRI01 data
collection instrument such that the coordinators or research staff would only key the data at discharge or status. My bad. In addition, it appears that folks are either forgetting to key the MRI01 data altogether or they are simply not enrolling patients in the secondary (which we will figure out for sure with this next round of emails). Therefore, I don't have a clear picture about the "real time"

enrollment, and I can't run after the sites to find out what the problem is, or to get them to enroll more agressively without that information.

So, my suggestion would be to insert a question "Was the infant enrolled in the SUPPORT Neuroimaging secondary" in the SUPP02, form
section D, as question #2 (right at the end). The only problem I foresee with this question is that, to date, 4 of the sites will be or are using separate consent forms for the secondary (rather than embedded). Thus, some of the sites may not actually get that consent right away. This might need to be flagged as an edit - some sites may need to go back and complete that question later.

What do you think of this idea? I have already talked with Abhik about the possibility of adding another question and he sounded like it was do-able. If you OK it, I will work with RTI to get it inserted.

The other thing I am doing with RTI is changing the way they are reporting the tracking for the Neuro secondary. I think with the additional question, and reporting MRI01 keyed status and MRIs and CUS received BY CENTER, folks will be a bit more motivated to get it
done.

Thanks for your input Neil,

Susan
--
Susan R. Hintz, M.D., M.S. Epi
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]
Cc: mcw3@po.cwru.edu; Wade Rich
Subject: RE: SUPPORT Stopping Rules
Date: Saturday, July 01, 2006 11:36:16 AM

Thanks Rose

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 30, 2006 12:11 PM
To: Neil Finer
Cc: mcw3@po.cwru.edu; Wade Rich
Subject: RE: SUPPORT Stopping Rules

Neil
The "rules" are those of NICHD. The DSMC communicates to the director who will make a decision and inform the program folks who inform the investigators.
I attached the changes.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, June 28, 2006 7:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: mcw3@po.cwru.edu; Wade Rich
Subject: RE: SUPPORT Stopping Rules

Hi Rose
I understand this but thought that we were writing for the SUPPORT Protocol. I had asked previously if we could make such comments or if the stopping rules were those of the NICHD, and not any individual study. If the latter is the case, we would need to ask whether they can be altered by specific study input. In addition we need clarification of what should be said in the actual Protocol/Manual.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 28, 2006 9:26 AM
To: Neil Finer
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil
There is a problem with the STOPPING RULES section.

The DSMC makes a recommendation to the Director of NICHD who makes the decision to stop or continue a trial. The investigators and program scientist do not attend these meetings and the DSMC acts independently of those vested in the trial. We need to amend this section of the minutes to reflect this NICHD mechanism for DSMCs.

I have some suggestions and can send them to you or discuss by phone. We need to have, in place, a mechanism to continue one arm if the other is halted.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, June 27, 2006 6:11 PM
To: Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone
Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.
Regards
Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

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Monday, June 19
12:00-1:00pm ET

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

Agenda
Trial Progress
New Site Orientation
Recruitment
SUPP05 Form - Newman
New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From: Susan Hintz
To: nxs5@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT MRI
Date: Friday, June 30, 2006 1:55:11 PM

Thanks so much for your hard work Nancy!!

Susan

Susan R. Hintz, M.D., M.S. Epi
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

> Excellent!!!!
> Thanks
>
> Rose

> **From:** Nancy Newman [mailto:nxs5@case.edu]
> **Sent:** Friday, June 30, 2006 12:55 PM
> **To:** Higgins, Rosemary (NIH/NICHD) [E]
> **Cc:** 'Michele Walsh'; 'Zaterka-Baxter, Kristin'
> **Subject:** RE: SUPPORT MRI
>
> Hi Rose- We have consented 8 patients for MRI and have performed 4 studiesŠŠŠ.NN

> **From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> **Sent:** Thursday, June 29, 2006 3:09 PM
> **To:** Michele Walsh; nxs5@cwru.edu; wcarlo@peds.uab.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; Pablo Sanchez; Walid Salhab; Nancy Miller; Gaynelle Hensley; alaptook@WIHRI.org; Angelita Hensman; M Bethany Ball; David Stevenson; Tyson, Jon E; Brenda.H.Morris@uth.tmc.edu; Mcdavid, Georgia E; Ronald N Goldberg; Kathy J Auten; Michael Cotten
> **Cc:** Susan Hintz; Zaterka-Baxter, Kristin
> **Subject:** SUPPORT MRI
>
> Your site has indicated that IRB approval has been granted for the SUPPORT Neuroimaging secondary.

Please respond to the following questions **by July 5th**:

How many patients have been enrolled in the Neuroimaging secondary at your site?

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet?

Also, as a reminder, we are asking that study-related MRI's and cranial US be sent to RTI *routinely* - the manual indicates that neuroimaging CD's should be sent to RTI *monthly*, although this may not be necessary for all sites depending on the volume of enrollment. The reason we have requested that neuroimaging be sent routinely is two-fold: 1) this procedure will facilitate "rolling" central reading, particularly of the MRI's, and 2) it is likely to be easier for sites to obtain CD duplicates of studies soon after they are completed rather than at the end of the trial.

Below is the section of the manual pertaining to preparing and sending neuroimaging studies.

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 (Digital Imaging and Communications in Medicine) 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.*

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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.

Kristin Zaterka-Baxter

4426 South Miami Blvd.

Durham, NC 27703

919-485-7750

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

Content-Type: image/gif;
name="image001.gif"
Content-ID: <image001.gif@01C69C44.71ED15B0>
Content-Description: image001.gif
Content-Location: image001.gif

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From: Neil Finer
To: Michele Walsh; Petrie, Carolyn; wcarlo@peds.uab.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Friday, June 30, 2006 10:31:54 AM

Michelle
Your table looks great. I will ask Marie to so tabulate.
Many thanks
Neil

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, June 29, 2006 12:38 PM
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
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Be well, Michele

> ----- Original Message -----
> **From:** Neil Finer
> **To:** Neil Finer ; Petrie, Carolyn ; wcarlo@peds.uab.edu ; Michele Walsh ; Bradley Yoder ; Roger Faix ; alaptook@WIHRI.org ; kurt.schibler@cchmc.org ; Higgins, Rosemary (NIH/NICHD) [E] ; Das, Abhik ; Poole, W. Kenneth ; nxs5@cwru.edu ; Wade Rich ; Gantz, Marie
> **Cc:** Zaterka-Baxter, Kristin ; cdg2749@yahoo.com ; msumner@peds.uab.edu ; Fernando Martinez ; bvecchio@careNE.org ; Webb, Robin E. ; Wade Rich
> **Sent:** Tuesday, June 27, 2006 6:15 PM
> **Subject:** RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
>
> Hello Again
> Here are 2 attachments regarding protocol deviations.
> I think that these are self-explanatory.
> Please share any comments.
> Thanks
> Neil
>
> ---
>
> **From:** Neil Finer
> **Sent:** Tuesday, June 27, 2006 3:05 PM
> **To:** 'Petrie, Carolyn'; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
> **Cc:** Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; Fernando Martinez;

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Cc: Zaterka-Baxter, Kristin; (b) (6); msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
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Recruitment
SUPP05 Form - Newman
New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From: Kathy J Auten
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Ronald N Goldberg; Michael Cotten; Kathy Foy
Subject: Re: Fw: SUPPORT MRI - Ctr 19 reply
Date: Friday, June 30, 2006 9:22:22 AM

Ctr 19 reply:

How many patients have been enrolled in the Neuroimaging secondary at your site? **None to date**

If your site has enrolled patients, has your site performed any study-related brain MRI's or cranial US yet? **N/A**

Kathy J. Auten, 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

Ronald N Goldberg <goldb008@mc.duke.edu> wrote on 06/29/2006 05:20:24 PM:

> ----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on
> 06/29/2006 05:19 PM -----
>
> "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
> 06/29/2006 03:09 PM
>
> To
>
> "Michele Walsh" <mcw3@case.edu>, <nxs5@cwru.edu>, <wcarlo@peds.uab.
> edu>, <mcollins@peds.uab.edu>, <scosby@peds.uab.edu>, "Pablo
> Sanchez" <Pablo.Sanchez@UTSouthwestern.edu>, "Walid Salhab" <Walid.
> Salhab@UTSouthwestern.edu>, "Nancy Miller" <Nancy.
> Miller@UTSouthwestern.edu>, "Gaynelle Hensley" <Gaynelle.
> Hensley@UTSouthwestern.edu>, <alaptook@WIHRI.org>, "Angelita
> Hensman" <AHENSMAN@CareNE.org>, "M Bethany Ball" <mbball@stanford.
> edu>, "David Stevenson" <dstevenson@stanford.edu>, "Tyson, Jon E"
> <Jon.E.Tyson@uth.tmc.edu>, <Brenda.H.Morris@uth.tmc.edu>, "Mcdavid,
> Georgia E" <Georgia.E.McDavid@uth.tmc.edu>, "Ronald N Goldberg"
> <goldb008@mc.duke.edu>, "Kathy J Auten" <auten002@mc.duke.edu>,
> "Michael Cotten" <cotte010@mc.duke.edu>
>
> cc
>
> "Susan Hintz" <srhintz@stanford.edu>, "Zaterka-Baxter, Kristin"
> <kzaterka@rti.org>
>
> Subject
>
> SUPPORT MRI
>
>
>
>
> Your site has indicated that IRB approval has been granted for the
> SUPPORT Neuroimaging secondary.
>
> Please respond to the following questions by July 5th:
>
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> at your site?
>
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> study-related brain MRI's or cranial US yet?
>

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> cranial US be sent to RTI routinely - the manual indicates that
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> not be necessary for all sites depending on the volume of
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> Each CD must be labeled with the following information:
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> 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.
>
> Kristin Zaterka-Baxter
> 4426 South Miami Blvd.
> Durham, NC 27703
> 919-485-7750
>
> [image removed]
>
>
>
>
> 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: Michele Walsh
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: Re: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Thursday, June 29, 2006 4:38:13 PM
Attachments: Protocol Deviations Table suggest.doc

Neil:
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Protocol Deviations: Ventilation Arm

Deviation	**CPAP**	**Control**
Consent Errors		
Randomization errors		
Assigned arm not implemented		
If intubated, surf not given in < 1 hr.		
Mechanical ventilation initiated w/o meeting criteria		
NSIMV w/o intubation		
Extubated b4 study criteria		
Failed to extubate at study criteria		

Protocol Deviations: Oximetry Arm

Deviation	**85-90%**	**91-95%**
Consent Errors		
Randomization errors		
Assigned arm not implemented		
Study Oximeter removed early		
Unmasked oximeters used.		

From: Angelita Hensman
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Abbot Laptook
Subject: RE: SUPPORT MRI
Date: Thursday, June 29, 2006 3:19:43 PM

Answers below.
Thanks
Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 29, 2006 3:09 PM
To: Michele Walsh; nxs5@cwru.edu; wcarlo@peds.uab.edu; mcollins@peds.uab.edu; scosby@peds.uab.edu; Pablo Sanchez; Walid Salhab; Nancy Miller; Gaynelle Hensley; Abbot Laptook; Angelita Hensman; M Bethany Ball; David Stevenson; Tyson, Jon E; Brenda.H.Morris@uth.tmc.edu; Mcdavid, Georgia E; Ronald N Goldberg; Kathy J Auten; Michael Cotten
Cc: Susan Hintz; Zaterka-Baxter, Kristin
Subject: SUPPORT MRI

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Durham, NC 27703
919-485-7750

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: M Bethany Ball
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: dstevenson@stanford.edu; sr hintz; vanmeurs@stanford.edu
Subject: Re: SUPPORT MRI
Date: Thursday, June 29, 2006 11:22:27 PM

Hi Rose,
For Stanford:

How many patients have been enrolled in the
Neuroimaging secondary at your site? 4

If your site has enrolled patients, has your site
performed any study-related brain MRI's or
cranial US yet? yes study-related (not standard
of care) HUS: 1
clinically indicated (SOC) MRIs: 2
patients in-house with MRI/late HUS pending: 2
patients with early HUS: 4

Discs sent to RTI: 0

Regards,
Beth

>Your site has indicated that IRB approval has
>been granted for the SUPPORT Neuroimaging
>secondary.
>
>Please respond to the following questions by July 5th:
>
>How many patients have been enrolled in the
>Neuroimaging secondary at your site?
>
>If your site has enrolled patients, has your
>site performed any study-related brain MRI's or
>cranial US yet?
>
>Also, as a reminder, we are asking that
>study-related MRI's and cranial US be sent to
>RTI routinely - the manual indicates that
>neuroimaging CD's should be sent to RTI monthly,
>although this may not be necessary for all sites
>depending on the volume of enrollment. The
>reason we have requested that neuroimaging be
>sent routinely is two-fold: 1) this procedure
>will facilitate "rolling" central reading,
>particularly of the MRI's, and 2) it is likely
>to be easier for sites to obtain CD duplicates
>of studies soon after they are completed rather
>than at the end of the trial.
>
>Below is the section of the manual pertaining to
>preparing and sending neuroimaging studies.

>
>
>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 (Digital
>Imaging and Communications in Medicine) 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.
>
> Removing PHI from digitized images
>may be difficult for some centers. Radiology
>departments at most centers can create duplicate
>"anonymous exams" on their systems; these
>"anonymous exams" may then be copied to CD. This
>procedure, which removes PHI from the image
>headers, has been particularly useful in
>previous MRI-related research. Radiology
>departments at other centers may use software
>that allows for alteration or "blacking out" of
>PHI headers after images are transferred to CD.
>However, if these options are not available at
>your center, additional language could be added
>to the secondary consent form explaining that
>central readers will interpret the images, which
>include headers, but will not have other
>information about the patient. Each center will
>need to work with their individual Radiology
>departments, and follow the requirements of
>their IRB with respect to the consent process.
>
>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.
>
>
>
>Kristin Zaterka-Baxter
>
>4426 South Miami Blvd.
>Durham, NC 27703
>919-485-7750

>
>
>
>
>
>
>Rosemary D. Higgins, M.D.
>Program Scientist for the Neonatal Research Network
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>301-496-3790 (FAX)
><mailto:higginsr@mail.nih.gov>higginsr@mail.nih.gov
>
>
>Content-Type: image/gif;
> name="image001.gif"
>Content-ID: <image001.gif@01C69B8D.B190F900>
>Content-Description: image001.gif
>Content-Location: image001.gif

From: Neil Finer
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Thursday, June 29, 2006 10:10:00 AM

Abhik
I would assume that we would not be able to time the events from the GDB. If true then a comparison would be difficult.
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, June 29, 2006 5:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Rose and Neil:

Sounds like this could be an interesting analysis. Please note that even though the SUPPORT AE form only collects AEs that happen in the first 14 days, Marie also looks at the GDB data to pick up all corresponding AEs entered in the GDB, regardless of when they happen. Of course, we may not have complete GDB or SUPPORT data on all these infants yet.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 29, 2006 9:38 AM
To: Neil Finer
Cc: Das, Abhik
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil
I spoke to Abhik – we may not have all of the adverse events as of yet. One other difference is that these are events that occur by day 14 (not the entire length of the GDB stay).

If we want to follow this prospectively, we should develop a secondary (I can do a draft) for the subcommittee.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 29, 2006 9:29 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hi Rose
According to previous studies infants in the control arms do better than previous historical controls and this appears to be true of any intervention. I suspect it is because of attention to detail and following protocol as was demonstrated for Adult RDS by the Salt Lake group. I think that the question of bias will be relatively easy to answer in the Network as those eligible but not enrolled are in GDB. As there are few absolute exclusion criteria ie malformations and DNR situations, the majority are not entered

because of lack of consent. This should be information that is available. Can Abhik look at this for one full year comparing the enrolled infants with the non-enrolled who were in the gestational age windows? I suspect that the best year to pick would be next year – hopefully!
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 29, 2006 4:54 AM
To: Neil Finer
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

I have a few other thoughts on this subject – are we selecting a "biased" population in the trial that inherently does better? Or is the fact that they are in a trial actually generating less adverse events? I can discuss with Abhik and ask him to see if we have those adverse event rates for the entire 24-27 week population in the GDB – this may be a good secondary study for the trial.

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, June 28, 2006 7:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hi Rose
It's always been said that individuals in trials do better. I will look for your comments.
I think that we can have a meeting which I will try to attend via telephone and then Wally or Michele can report to the Steering Committee or I could by Phone conference if you prefer.
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 28, 2006 9:50 AM
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) [redacted]; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

HI,
Perhaps we can share these with the steering committee at the July meeting. One note of observation – The percent of SUPPORT infants with adverse events appear to be lower (across the board for each type of event and each gestational age strata with the exception of air leak in the 26-27 week infants) than for the NRN in the baseline data. I realize this is a "historical control" but it is interesting.
I have some comments on the stopping rule paragraph and will send them in the next day or so.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, June 27, 2006 6:15 PM
To: Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; (b) (6); msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Again
Here are 2 attachments regarding protocol deviations.
I think that these are self-explanatory.
Please share any comments.
Thanks
Neil

From: Neil Finer
Sent: Tuesday, June 27, 2006 3:05 PM
To: 'Petrie, Carolyn'; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6); msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone
Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.
Regards
Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6); msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Reminder for Monday's call

The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19
12:00-1:00pm ET

To join the call,

Dial Toll Free, **866-675-**(b) (6)
Passcode: (b) (6)

Agenda
Trial Progress
New Site Orientation
Recruitment
SUPP05 Form - Newman

New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From: Neil Finer
To: Bradley Yoder
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Wednesday, June 28, 2006 7:14:36 PM

Hi Brad
Hi Brad
Let's plan for Thursday the 27th of July. I believe that I can get in around 10:30 AM and get to the hospital by 11:30 I would need to leave by 5:00 for a 6:40 flight.
I think that there may be an earlier flight and I will check which would give more time if needed.
I would think that it would be appropriate for us to meet with your nursing and respiratory staff, and then a separate meeting with medical staff including fellows, and research staff, especially if they are going to get consents and care for infants in the DR.
We could have one of these as a lunch meeting and the other to follow. I would plan that each presentation would take at least 1h 30 minutes, but depending on your staff this could be shorter. I think we should plan for longer to try to answer questions. Wade and I have done this together and I found that was the best approach.
I would suggest that Wade also come and spend at least 2-3 hours with your co-ordinator(s) to discuss various aspects of the trial and the data forms. I believe that Rose would probably want our travel arranged and paid for by your center and we will not require accommodation. This is what worked best for us in the past. In addition you will have study oximeters there by then and Wade would run through doing a download and setting them up.
Let me know if this sounds OK to you.
Be well
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Wednesday, June 28, 2006 11:04 AM
To: Neil Finer
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil:
Given vacation, meeting & work schedules here, the best week is that of 24-28 July.
Any day(s) are fine with us...so let me know what is best for you & how you want to work this.

Brad

>>> "Neil Finer" <nfiner@ucsd.edu> 6/27/2006 9:10:46 PM >>>
Hi Brad
Can you suggest some possible dates? Thursday and Fridays are best for me at present.
I will ask Rose to get you some oximeters.
Neil

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

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Tuesday, June 27, 2006 6:34 PM
To: Neil Finer
Cc: higginsr@mail.nih.gov
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil:
No problems with what or how you said it.
We have preliminary approval from both our major delivery hospitals.
Hope to have final approval in next couple weeks.
Could we plan on getting oximeters & visit in July?
I will be out of town (b) (6) .

Thanks.

Brad

Bradley A. Yoder, MD
Professor of Pediatrics
University of Utah School of Medicine
Dept of Pediatrics/Neonatology
PO Box 581289
Salt Lake City, UT 84158-1289

Phone: 801-581-7052
Pager: 801-339(b) (6)
FAX: 801-585-7395
Email: bradley.yoder@hsc.utah.edu

For courier delivered mail, the physical address is:

Williams Building
295 Chipeta Way, Room 2N114
Slat Lake City, UT 84108
>>> "Neil Finer" <nfiner@ucsd.edu> 06/27/06 4:10 PM >>>
Hello Everyone

Please find attached minutes of previous conference call. I have added
a
suggested paragraph regarding Stopping individual arms of the SUPPORT
trial. Please make any changes you feel would be helpful, and let me
and
Rose have your comments/suggestions.

Regards

Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh;
Bradley Yoder; Roger Faix; alaptook@WIHRI.org;
kurt.schibler@cchmc.org;

Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth;
nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu;
Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

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Dial Toll Free, 866-675-(b) (6)

Passcode: (b) (6)

Agenda

Trial Progress

New Site Orientation

Recruitment

SUPP05 Form - Newman

New business

We are not using the fancy presentation system, so this will be a
regular conference call with the SUPPORT Subcommittee.

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: MRI Secondary to Support
Date: Wednesday, June 28, 2006 3:55:33 PM

Ouch.

>I will send them tomorrow - (b) (6)
>Thanks
>Rose
>--------------------------
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
>>From: Susan Hintz <srhintz@stanford.edu>
>To: Zaterka-Baxter, Kristin <kzaterka@rti.org>
>Cc: Higgins, Rosemary (NIH/NICHD) [E]
>Sent: Wed Jun 28 15:12:33 2006
>Subject: Re: FW: MRI Secondary to Support
>
>Rose
>See below for Wayne. Please edit my email drafts for that too -
>
>Thanks
>
>susan
>
>
> Hi,
>
> Please see below for Wayne States response. They will participate.
>
> Thanks,
>
> Kris
>
>
>
>
>
> Kris Zaterka-Baxter, RN, CCRP
>
> RTI International
>
> 4426 South Miami Blvd.
>
> Durham, NC 27703
>
> Telephone: (919) 485-7750
>
> Fax: (919) 485-7762
>
> kzaterka@rti.org
>

>
>
>
>
> -----Original Message-----
> From: Rebecca Bara [mailto:ae5357@wayne.edu]
> Sent: Wednesday, June 28, 2006 2:36 PM
> To: Zaterka-Baxter, Kristin
> Subject: Re: MRI Secondary to Support
>
>
>
> Hi Kris,
>
>
>
> We do plan to participate in the MRI secondary. It's gone to
>IRB as an amendment to the main trial but with a stand-alone
>consent--no approval yet.
>
>
>
> Thanks,
>
> Becky
>
>
>
> ---- Original message ----
>
> >Date: Wed, 28 Jun 2006 12:45:30 -0400
>
> >From: "Zaterka-Baxter, Kristin" <kzaterka@rti.org>
>
> >Subject: MRI Secondary to Support
>
> >To: "Rebecca Bara" <ae5357@wayne.edu>
>
> >
>
> > Hi Becky,
>
> >
>
> > I'm following up on a query from March re. the MRI
>
> > secondary to Support. Are you participating in this
>
> > secondary and if so, was it rolled into the main
>
> > support trial? If yes to either, or if approved
>
> > separately, can you email me your approval date and
>
> > fax your approval and consent when you have a sec.
>
> >

> Thanks a ton.
>
> Kris
>
>
>
>
> Kris Zaterka-Baxter, RN, CCRP
>
> RTI International
>
> 4426 South Miami Blvd.
>
> Durham, NC 27703
>
> Telephone: (919) 485-7750
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> Fax: (919) 485-7762
>
> kzaterka@rti.org
>
>
>
>
> This message and any files transmitted with it may contain
>information that is privileged, confidential and exempt from
>disclosure. It is intended for use only by the person to whom it is
>addressed. If you have received this in error, please (1) do not
>forward or use this information in any way, (2) delete or destroy
>this message and its attachments and (3) please contact me
>immediately.
>
>

From: Susan Hintz
To: Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Re: MRI Secondary Study to Support
Date: Wednesday, June 28, 2006 3:10:08 PM

Rose,

1) Please edit my email to **Case** - they are approved so Case can get the email for the approved group.
2) Also, it looks like Cincinnati will not be participating - so please take Cinncinati off the email list.

Thanks

Susan

Hi,

Please see below. Cincinnati will not be participating in the MRI 2*. I've also heard from Case (05/11/06). They are approved and it is a separate consent.

Thanks,

Kris

Kris Zaterka-Baxter, RN, CCRP

RTI International

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Estelle Fischer [mailto:Estelle.Fischer@cchmc.org]
Sent: Wednesday, June 28, 2006 1:11 PM
To: Zaterka-Baxter, Kristin
Cc: Cathy Grisby
Subject: Fwd: Re: MRI Secondary Study to Support

Hi Kris:

Cathy had indicated that you left a v-mail....concerning information about our site particpating in the MRI Secondary....

Unfortunately, we are not able to participate....

Please see email (sent to you on 3/31) for an explanation as to why our site is not able to participate...

Please feel free to contact Dr. Schibler, should you need additional information.

Thanks,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.558.0005 Fax: 513.558.7770

>>> Estelle Fischer 03/31/06 2:46 PM >>>

Hi Kris:

RE: Participation in the MRI Secondary Study

After discussing the feasiblity of conducting this protocol, with a Raidologist and MRI Imaging Technician, in the Imaging Research Center (IRC) at our institution, we have decided that there are too many logistical issues that would prohibit our ability to participatie in this study.

The main limitations, as offered by Dr. Blaise Jones and Kendall O'Brien, R.T. , from the IRC are as follow:

>1. It is doubtful that high quality images could be consistently
>achieved on our infants at 35 to 42 weeks gestational age.

>2. Sedation for these images is not an option. The IRB would not allow it
>and subjects receiving sedation would need to be admitted for observation
>overnight.

>3. Safety for infants undergoing scanning is responsibility of PI for
>research scans.

>4. Research imaging slots are limited. A scan without sedation scan on an
>infant would likely be performed last in case additional time is required.

Thus, we, unfortunately, are not able to particpate.

If you have any questions, please feel free to contact Dr. Schibler or Cathy Grisby.

Thank you,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.558.0005 Fax: 513.558.7770

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 03/24/06 11:38 AM >>>

Hi all,

With the reactivation of SUPPORT enrollment in February and the Steering Committee meeting approaching, we would like information about participation in the SUPPORT Neuroimaging secondary to be as complete as possible. We have not yet heard definitively from your site about whether you are planning to participate in this secondary.

Please respond to the following:

1. Has your site received IRB approval for the SUPPORT Neuroimaging secondary?

If yes, what was the approval date?

2. If your site has received IRB approval or approval is pending, will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall study consent?

3. If your site has not received IRB approval, has your site applied for IRB approval for the SUPPORT Neuroimaging secondary?

If not, does your site intend to participate?

4. If your site does not intend to participate, what were the main limitations for participation?

Thanks for your time,

Kris

Kris Zaterka-Baxter, RN, BSN, CCRP

RTI International

Statistics and Epidemiology

4426 South Miami Blvd.

Durham, NC 27703

Telephone: (919) 485-7750

Fax: (919) 485-7762

kzaterka@rti.org

From: Zaterka-Baxter, Kristin
To: Wade Rich
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Schaefer, Scott E.; Gantz, Marie; Das, Abhik
Subject: Masimo shipment
Date: Wednesday, June 28, 2006 2:50:54 PM

Hi Wade,
Below are the masimo serial numbers I have for UCSD. You actually have 36 including the latest set of 10 sent in November 2005. Please verify these are correct. If so, please send all 36 to the University of Utah care of:

Susan Tepper
University of Utah
Division of Neonatology, Department of Pediatrics, University of Utah School of Medicine
295 Chipeta Way
Salt Lake City, UT 84108

I have notified Susan that they are coming this week or next. When sending the oximeters (and docking stations), please send them next day delivery and forward me the tracking number.

310820	orange
310826	orange
310850	orange
310875	blue
310892	orange
310937	blue
310943	orange
310963	blue
310974	orange
310989	blue
310994	blue
310997	blue
311138	orange
311145	blue
311146	blue
311157	orange
318351	blue
318358	orange
318364	orange
318389	blue
318541	orange
318550	blue
318844	orange
318848	blue
318849	orange
318859	blue
320520	orange
320521	orange

320526	orange
320530	orange
320531	orange
320524	blue
320525	blue
320527	blue
320528	blue
320529	blue

Thanks a ton for helping us out, it is truly appreciated. The masimo's will be returned to you at the end of the study. Please keep your laptop as well. Please also remember to erase all stored materials on the laptop associated with the Support study prior to any further use.

Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
To: linda_reubens@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Schaefer, Scott E.; Gantz, Marie; Das, Abhik
Subject: Masimo oximeter shipment
Date: Wednesday, June 28, 2006 2:31:57 PM

Hi Linda,
Below are the masimo serial numbers I have for Rochester. Please verify these are correct. If so, please send all 8 to Iowa University care of:

Karen Johnson
University of Iowa
Department of Pediatrics
200 Hawkins Drive, 8900 JPP
Iowa City, IA 52242

I have notified Karen that they are coming this week or next. When sending the oximeters (and docking stations), please send them next day delivery and forward me the tracking number.

310717	BLUE
310723	ORANGE
310724	ORANGE
310729	ORANGE
310734	BLUE
310748	BLUE
323024	ORANGE
320283	BLUE

Thanks a ton for helping us out, it is truly appreciated. The masimo's will be returned to you at the end of the study.

- The laptop is yours! Please erase all stored materials on the laptop associated with the Support study prior to any further use.

Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Tyson, Jon E
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ***Urgent FW: Sat monitors,Support study
Date: Wednesday, June 28, 2006 11:20:46 AM

Georgia says we have only 4 blue monitors. With (b) consented here, it may be better to contact another site.

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 28, 2006 10:17 AM
To: Tyson, Jon E
Cc: Mcdavid, Georgia E
Subject: RE: ***Urgent FW: Sat monitors,Support study

These (b) (6) were consented last week at 24 1/7 weeks. I don't have further information other than the fact that she remains in the hospital. If you can't spare one, I can contact another site.

Thanks
Rose

-----Original Message-----
From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Wednesday, June 28, 2006 11:15 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Mcdavid, Georgia E
Subject: RE: ***Urgent FW: Sat monitors,Support study

Georgia has consent from (b) as well and is going to check on their status and we'll let you know. Is delivery imminent for the (b) in Dallas?

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: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 28, 2006 10:08 AM
To: Tyson, Jon E; Reardon, Alice J; Morris, Brenda H; Mcdavid, Georgia E

Subject: ***Urgent FW: Sat monitors,Support study
Importance: High

Can you folks spare one blue oximeter for the Dallas site? Let me know in the next hour if possible.
Thanks
Rose

-----Original Message-----
From: Gaynelle Hensley [mailto:Gaynelle.Hensley@UTSouthwestern.edu]
Sent: Wednesday, June 28, 2006 11:05 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Sat monitors,Support study

Rose, I need one blue sat monitor. I still have the (b) (6) consented.
We enrolled 2 more babies last weekend
I have 3 blue and 4 orange
If you need to call please call 214648(b) (6)
Thanks Gay

From: Das, Abhik
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Wednesday, June 28, 2006 10:02:11 AM

I think we can send them everything with the stated proviso that they only enroll after receiving all approvals.

Thanks

Abhik

-----Original Message-----
From: Zaterka-Baxter, Kristin
Sent: Wednesday, June 28, 2006 7:10 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Das, Abhik
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hi,
Be happy to. Can I also send them the randomization packages (cards etc.)? I've not received either sites IRB approval yet but if that's fine, I can send.
Thanks,

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 28, 2006 6:25 AM
To: Zaterka-Baxter, Kristin
Cc: Das, Abhik
Subject: Fw: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Kris
Can you arrange the Utah and also Iowa oximeters to be sent?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'Bradley.Yoder@hsc.utah.edu' <Bradley.Yoder@hsc.utah.edu>
Sent: Wed Jun 28 06:23:52 2006
Subject: Re: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Terrific. I will have Kris make arrangements for oximeters.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Neil Finer <nfiner@ucsd.edu>
To: Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Jun 27 22:10:46 2006
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hi Brad
Can you suggest some possible dates? Thursday and Fridays are best for me at present.
I will ask Rose to get you some oximeters.
Neil

-----Original Message-----
From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Tuesday, June 27, 2006 6:34 PM
To: Neil Finer
Cc: higginsr@mail.nih.gov
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil:
No problems with what or how you said it.
We have preliminary approval from both our major delivery hospitals.
Hope to have final approval in next couple weeks.
Could we plan on getting oximeters & visit in July?
I will be out of town (b) (6)

Thanks.

Brad

Bradley A. Yoder, MD
Professor of Pediatrics
University of Utah School of Medicine
Dept of Pediatrics/Neonatology
PO Box 581289
Salt Lake City, UT 84158-1289

Phone: 801-581-7052
Pager: 801-339 (b) (6)
FAX: 801-585-7395
Email: bradley.yoder@hsc.utah.edu

For courier delivered mail, the physical address is:

Williams Building
295 Chipeta Way, Room 2N114
Slat Lake City, UT 84108
>>> "Neil Finer" <nfiner@ucsd.edu> 06/27/06 4:10 PM >>>
Hello Everyone

Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.

Regards

Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Reminder for Monday's call

The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19

12:00-1:00pm ET

To join the call,

Dial Toll Free, 866-675(b) (6)

Passcode: (b) (6)

Agenda

Trial Progress

New Site Orientation

Recruitment

SUPP05 Form - Newman

New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From:	Neil Finer
To:	Neil Finer; Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc:	Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject:	RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date:	Tuesday, June 27, 2006 6:15:17 PM
Attachments:	Protocol deviations involving oximeters 6-27-06.doc SUPPORT Protocol Deviations and AEs 6-19-06.doc

Hello Again
Here are 2 attachments regarding protocol deviations.
I think that these are self-explanatory.
Please share any comments.
Thanks
Neil

From: Neil Finer
Sent: Tuesday, June 27, 2006 3:05 PM
To: 'Petrie, Carolyn'; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Hello Everyone
Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.
Regards
Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

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Details of SUPPORT protocol deviations involving non-study oximeters or removal of study oximeter
6-27-06

Protocol deviation description	Circumstances	Comments
Infant placed on unit pulse oximeter.	Parents rooming in prior to discharge. Infant placed on unit pulse oximeter in room with parents.	
pulse oximetry applied, not study oximetry.	see F9	
potential for unblinding oximeter assignment.	a non-study pluse oximeter was inadvertently placed on the infant (in addition to my study oximeter) to obtain pre and post-ductal saturations.	non-study pluse ox was placed on 6/10/06. at 10:30 am, then removed on 6/12/06 at 10:30 am (when study staff became aware of situation).
Non-study oximeter placed on infant	Concern for PPHN for this infant. Placed on upper and lower Sat monitors. One study oximeter, one non-study oximeter.	Non-study oximeter removed on 8/22/05.
Non-study pulse oximeter placed when pre & post p.o. needed.	Baby sick & required pre & post ductal monitoring. Staff placed non-study pulse oximeter for post ductal readings instead of same color study pulse oximeter.	Non-study pulse oximeter DC on 3/17/05
infant off study monitor	baby transferred to another facility on 12/6/05 at 1207. returned to this facility on 12/7/05 at 0216and was placed on non-study monitor.	infant placed on study monitor on 12/7/05 at 1125
study pulse oximeter removed	Baby moved from c-bay to ccn. placed on non-study pulse oximeter. new study pulse oximeter placed 10/27/05 @0850	baby in NC 2L flow, RA. 36 wk date 11/4/05
study oximeter restarted	study oximeter restarted 2 to transfer cancelled	
magimo not re-initiated	baby went back on oxygen over the weekend and masimo was not put back on.	masimo placed on 9/19/05
study oximeter not placed back on baby when baby placed back in NC.	study oximeter removed 11/28/05 per protocol. Baby placed back into NC. 1< flow on 11/30/05 @ 0550 and was not placed back into study oximeter.	Study oximeter placed 11/30/05 @0940,
Study oximeter removed while infant was still on oxygen.	study oximeter removed while still on oxygen.the infant was off from 4/9 at 2100 to 4/12 at 0930. Both oximeters downloaded.	
Removed from study pulse oximeter @ 0400	Bedside nurse removed patient from study pulse ox during preparation for surgery. Subject placed back on study pulse oximeter 10/19/05 @ 0800.	
oximeter replaced with non-stody oximeter @ 2300	RN said study oximeter stopped working - replaced with another oximeter that was told was a study oximeter	study oximeter restarted 5/30 @ 2200
RN removed study oximeter too early	RN decided she didn't like the pulse ox and changed it to the monitor one.	patient was due to come off the oximeter at 1700 for 72 hrs on room air, pt placed back on oximeter until 1700, RN REEDUCATED on study protocols
oximeter discontnued before off all support	infant transfered to stepdown from dol #39 and study oximeter stopped. infant still on nciL21. Infant to be trsnferred to outside hospital dol #42 oximeter not restarted dol #41 when noted.	

SUPPORT Study Protocol Deviations and Adverse Events Reported as of June 19, 2006

Protocol Deviations

Code	Type of protocol deviation	Number
1	Infant intubated without meeting study criteria	0
2	CPAP not initiated if required by protocol	1
3	Surfactant not given in the first hour	4
4	Mechanical ventilation initiated for other than study criteria	0
5	NSIMV initiated in infant not previously intubated	2
6	Extubation (excluding unplanned) for other than study criteria	2
7	Failure to extubate CPAP infant if all criteria met	3
8	Infant received incorrect treatment assignment	2
	Incorrect treatment assignment sub-category: N	
	Ventilator strategy: 0	
	Oximetry strategy: 2	
	Total: 2	
9	Oximeter not started within 2 hours	4
10	Other	37
	Other AE specified: N	
	Non-study oximeter used/study oximeter removed early: 15	
	High flow nasal cannula used within first 14 days: 7	
	Decadron given: 3	
	Wrong envelope opened, or envelope opened early: 3	
	Baby withdrawn from study: 2	
	Infant randomized to control arm without consent: 1	
	Failure to extubate control arm infant when criteria met: 1	
	Infant intubated and surfactant given at 2 hours of life: 1	
	Hydrocortisone given days 20-21: 1	
	HUS done outside 4-21 day windown: 1	
	Study monitor placed on non-study baby: 1	
	Unknown: 1	
	Total: 37	
Total		55

Adverse Events

Percent of SUPPORT infants with selected adverse events*

Type of adverse event	All infants	24-25 wks	26-27 wks
Chest compressions/epinephrine in DR	5.1%	6.1%	4.4%
Air leak	7.7%	9.2%	6.6%
Pulmonary hemorrhage	5.9%	7.5%	4.6%
Severe IVH (grades III-IV)	12.7%	16.8%	9.2%

Percent of GDB infants with selected adverse events and range across NRN centers*
(Includes infants born at NRN centers (inborn) at 24-27 weeks GA in 2002-2004)

	All infants		24-25 wks		26-27 wks	
Type of adverse event	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine in DR	11.2%	3.2 - 31.8%	13.9%	2.8 - 42.1%	9.1%	3.2 - 23.2%
Air leak	8.2%	1.9 - 16.1%	11.0%	2.9 - 20.6%	6.1%	1.1 - 13.0%
Pulmonary hemorrhage	9.0%	3.4 - 29.3%	12.3%	2.5 - 32.0%	6.5%	1.1 - 26.9%
Severe IVH (grades III-IV)	16.9%	8.4 - 26.4%	24.2%	14.0 - 38.9%	11.7%	2.3 - 20.8%

*Denominator for chest compressions is number of infants with delivery room information, denominator for air leak and pulmonary hemorrhage is number of infants who survived 12 hours, denominator for severe IVH is number of infants with head ultrasound.

From: Neil Finer
To: Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.; Wade Rich
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Tuesday, June 27, 2006 6:11:10 PM
Attachments: Minutes June 19.doc

Hello Everyone
Please find attached minutes of previous conference call. I have added a suggested paragraph regarding Stopping individual arms of the SUPPORT trial. Please make any changes you feel would be helpful, and let me and Rose have your comments/suggestions.
Regards
Neil Finer

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) ; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
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The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19
12:00-1:00pm ET

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

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Trial Progress
New Site Orientation
Recruitment
SUPP05 Form - Newman
New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

Agenda for SUPPORT Subcommittee Meeting – June 19 2006

SUPPORT Subcommittee minutes June 19 2006
A meeting was held by teleconference of the SUPPORT Subcommittee.
The following items were discussed and reviewed.

1. Review Enrollments to date –about 290.
Leading enroller is Case Western, followed by UT Texas, Brown and Emory
We need to work with centers that have few enrollments and 3 active ongoing centers have < 5 enrollments from the beginning of the trial.
There were 19 enrollments in April, 10 in May.
We reviewed the proposed target numbers an agreed that the target should remain at 3 per center per month – 36/center/year. If we can achieve this rate we would enroll 570/year and be complete within a little over 2 years
The new centers have not yet begun to recruit and their involvement will help this process.

2. We discussed new centers site visits. Abbot and Michele will each do a visit to Boston and Iowa and I plan to visit Salt Lake and Albuquerque.

3. The Secondaries were discussed. The benefits of a common consent were discussed and it was felt that it may be better not to bundle the secondary studies in the SUPPORT consent with the main issue being presenting too much information to the family. The design of the site consents will remain a local site issue.
I think that it would be advantageous to have a brief meeting at the next Steering Committee to allow Tim Stevens and Susan Hintz to talk about their projects

4. Overall trial issues were reviewed. We discussed the modified Supp05
We do not have any additional oximeter data for circulation at the present as Marie is redoing the software. We may have more information by the time of the Steering Committee. The issue of consent for multiple pregnancies was reviewed, specifically for multiples consented and randomized but for which only 1 infant delivers. We agreed that the subsequent live born infants may be enrolled if they deliver in the window.
There was a general discussion about Stopping rules and stoppage of either arm in the trial.

5. We reviewed the current rules and we decided to add wording to the SUPPORT Study and Manual that would deal with such an instance
A suggestion of such wording follows. Please review and let me and Rose know if you are in agreement with this statement or would like to modify it in any way.

"Stopping Rules – SUPPORT Trial
Addendum
If circumstances arise during the SUPPORT trial that result in the DSMC recommending stoppage of the SUPPORT trial we would recommend the following procedures:

1. Immediate discussion with the PI/designate initiated by the Science Officer to determine if additional information would assist in the decision process
2. If the decision is to stop, then there should be clarity regarding whether there is harm/benefit for the overall study, or one or the other of the study arms.
3. If the stoppage is exclusively related to only one of the interventions, ie the Oximeter arm or the CPAP arm, then the recommendation would be for stoppage of only the arm associated with risk/benefit, and the other arm of the trial would continue enrolling.
4. There may be a need for the data center to recalculate the power of the remaining arm based on the enrollment status of the trial at that time.

Respectfully submitted
Neil Finer
PI for SUPPORT

From: Zaterka-Baxter, Kristin
To: Michele Walsh
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Fi02% adjustment for altitude
Date: Tuesday, June 27, 2006 5:56:09 PM

Hi,
Abhik thought an email to the centers affected by altitude would suffice with RTI statistician aware of the Fi02 adjustments as needed. If you would prefer a technical memo I can draft one and send it out for review prior to distribution. Just let me know.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Tuesday, June 27, 2006 5:17 PM
To: Zaterka-Baxter, Kristin; Bradley Yoder; Roger Faix; Kristi Watterberg; lLPapile@salud.unm.edu; Susan Tepper; Conra Backstrom
Cc: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; mcw3@cwru.edu; Das, Abhik; Gantz, Marie; Auman, Jeanette O.; Petrie, Carolyn
Subject: Re: Fi02% adjustment for altitude

Kris:
Who will prepare the technical memo?
Do you want me to do this?
Michele

> ----- Original Message -----
> **From:** Zaterka-Baxter, Kristin
> **To:** Bradley Yoder ; Roger Faix ; Kristi Watterberg ; lLPapile@salud.unm.edu ; Susan Tepper ; Conra Backstrom
> **Cc:** Higgins, Rosemary (NIH/NICHD) [E] ; nfiner@ucsd.edu ; mcw3@cwru.edu ; Das, Abhik ; Gantz, Marie ; Auman, Jeanette O. ; Petrie, Carolyn
> **Sent:** Tuesday, June 27, 2006 4:05 PM
> **Subject:** Fi02% adjustment for altitude
>
> Hi all,
> Thank you all for your time and the information sent. For recording Fi02 at high altitudes, please document the actual Fi02 for both the Support study and the New Physiologic Definition study and RTI will adjust for altitude in the analysis stage when the need arises. Please let us know if you have any questions.
> Thanks,
> Kris
>
> Kris Zaterka-Baxter, RN, CCRP
> RTI International
> 4426 South Miami Blvd.
> Durham, NC 27703

Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Susan Hintz
To: adas@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: more on SUPPORT Neuro secondary
Date: Tuesday, June 27, 2006 5:46:08 PM
Attachments: SUPPORTNeuroReport.xls
MRI Enrollment Form[MRI01]6-9-05.doc

Hi Abhik,

I have a few more questions about the SUPPORT Neuro secondary issues - just for you!

1) MRI 01 (enrollment form) programming (ATTACHED just in case you need it):
Is the MRI 01 programming up and working?
Have you received any comments about problems with this form?

2) Another PRELIMINARY question needed?
It occurs to me that, in my attempt to limit the number of forms and extra data collection that would be needed for the Neuro secondary, we do not have an "early warning system" to let us know if sites are falling behind in their projected enrollment for the secondary. Do you see this as a problem? The way I see it, right now we would not know whether someone was truly "consented" for the secondary until the MRI 01 was completed. And the MRI O1 would not need to be completed until all the neuroimaging was done (or tried but failed). Is there any place to ask an additional question in the coding for the MAIN trial - i.e., "SUPPORT Neuroimaging secondary consented" or similar?

3) Tracking report:
I think it would be helpful to us, and maybe give the sites a "nudge", if we could be more complete in the tracking report for the Neuroimaging secondary. I am attaching an excel spreadsheet as a potential template - but I would really like you to weigh in on it.

Thanks Abhik!

Susan
--
Susan R. Hintz, M.D., M.S. Epi
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

SITE	IRB approval date for SUPPORT Neuro secondary	# SUPPORT patients enrolled in MAIN TRIAL since secondary approval	# patients enrolled in Neuro secondary (MRI01 done vs. consent signed??)	# patients enrolled in Neuro secondary who have reached 35 weeks PCA	# MRIs received at RTI	# EARLY CUS received at RTI	# LATE CUS received at RTI
Alabama							
Case							
Dallas							
ETC, ETC....							

Draft Support Neuroimaging Secondary
Draft Enrollment/Tracking/Local Reader Form

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

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, June 27, 2006 5:11:47 PM

That sounds reasonable. For such an involved study, we should meet.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 27, 2006 5:03 PM
To: Petrie, Carolyn
Subject: FW: SUPPORT

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, June 27, 2006 5:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Hi Rose
I am currently composing some information for the committee. I see that a meeting has been placed on the agenda. It may be helpful for Tim and Susan to speak about their secondaries. They need to be cheerleaders for their studies. I will not be coming but will try to connect by conference phone if one can be made available. I will get my stuff back to you later today.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 27, 2006 12:41 PM
To: Neil Finer
Cc: Petrie, Carolyn
Subject: SUPPORT

Neil
Do you want us to schedule a support subcommittee meeting or can we forego it this time for the steering committee meeting?
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: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Poole, W. Kenneth; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: RE: Fi02% adjustment for altitude
Date: Tuesday, June 27, 2006 2:34:13 PM

Hi Abhik
I agree with your approach. I would like RTI to have the actual FiO2, and then apply any correction that may be necessary. I do not think that the individual sites should be making such corrections. In addition infants on one arm of the oximeter study may in fact reach room air even, at these altitudes.
Neil

From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, June 27, 2006 6:49 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Cc: Poole, W. Kenneth; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: RE: Fi02% adjustment for altitude

Rose and Neil:

Kris can check with NM about their data. As for what to do about this issue in SUPPORT, Ken and I were thinking that we would record the actual FiO2 that is read for these two sites (as we do for all other sites). We can always adjust Utah and New Mexico's readings at RTI in the analysis stage when the need arises. Let us know if this is your understanding as well, or this needs further clarification and discussion.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, June 27, 2006 10:34 AM
To: Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Cc: Das, Abhik
Subject: RE: Fi02% adjustment for altitude

We need to know if this is at altitude or corrected (i.e. < 25% = room air).

Thanks
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 27, 2006 10:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Das, Abhik
Subject: FW: Fi02% adjustment for altitude

Hi,
Please see below for the number of infants on 02 @ 36weeks at the NM Center.
Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Friday, June 23, 2006 5:40 PM
To: Zaterka-Baxter, Kristin
Cc: Backstrom, Conra; Papile, Lu-Ann
Subject: Re: Fi02% adjustment for altitude

Kris, the information we have is below, our 2005 data compared to VON 2004. As you can see, we have more kids on O2 in every category, but send them home as soon or sooner (on O2). The left hand column - all babies - shows that we have the same number in hospital at 36 weeks, but more on O2; in the VLBW, fewer are in hospital, more on O2.

Let me know if this is helpful, and what questions you have. Kristi

BPD		
	UNM	VON
In Hospital at Day 28	27%	22%
Oxygen at Day 28	64%	40%
Steroids for CLD	2%	2%
In Hospital at 36wks	38%	36%
Oxygen at 36wks AGA	44%	27%
Oxygen at Discharge/Transfer	21%	3%
Oxygen at Discharge to Home	20%	

VLBW - BPD		
	UNM	VON
In Hospital at Day 28	67%	74%
Oxygen at Day 28	54%	53%
Steroids for CLD	7%	9%
In Hospital at 36wks	46%	56%
Oxygen at 36wks AGA	65%	37%
Oxygen at Discharge/Transfer	45%	10%
Oxygen at Discharge to Home	55%	

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 6/22/2006 2:12 pm >>>
Hi,
Would it be possible to estimate what percent of infants are on oxygen at 36 weeks in your Centers?
Thanks,
Kris

Kris Zaterka-Baxter
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 22, 2006 7:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; Das, Abhik; Petrie, Carolyn; Fernando Martinez; Wade Rich
Subject: Fi02% adjustment for altitude

Hi,
For the Support study, Dr Yoder (Utah) has suggested the following adjustment in Fi02% to determine what is considered in room air at high altitudes (5000 feet) based on barometric pressure. This will affect Utah and NM. Below is the suggested adjustment:

"Adjust all the FiO2 variables by a factor of 1.22 to account for the altitude at SLC compared to the other centers. Thus, "21%" at sea level is equivalent to 21*1.22 or 25.6% at 5000 feet. For ease of use we will assume that infants in < 25% FiO2 would be in room air at sea level."

Thanks,
Kris

From: Neil Finer
To: Neil Finer
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT protocol deviations and AEs
Date: Tuesday, June 27, 2006 1:39:09 PM

HI Marie
Can you provide more detail about the following?

| Non-study oximeter used/study oximeter removed early | 15 |

This appears the commonest problem and I would like to know which of the possibilities existed; ie non-study vs early removal and any explanation for these 15 events.
Thanks
Neil

From: Neil Finer
Sent: Monday, June 26, 2006 8:56 AM
To: Wade Rich
Subject: FW: SUPPORT protocol deviations and AEs

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, June 20, 2006 9:48 AM
To: Neil Finer
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: SUPPORT protocol deviations and AEs

Hi Neil,

Attached is a document with the information you requested regarding SUPPORT protocol deviations and adverse events. 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

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Das, Abhik
Subject: FW: FW: Fi02% adjustment for altitude
Date: Tuesday, June 27, 2006 11:31:57 AM

Please see below.
Thanks,
Kris

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Tuesday, June 27, 2006 10:57 AM
To: Zaterka-Baxter, Kristin
Subject: Re: FW: Fi02% adjustment for altitude

These are clinical numbers - no corrections have been added.

>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 6/27/2006 8:37:48 am >>>
Thanks Dr. Watterberg,
Are the numbers below at altitude or corrected (i.e. < 25% = room air).
Much appreciated,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, June 27, 2006 10:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Das, Abhik
Subject: FW: Fi02% adjustment for altitude

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From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Friday, June 23, 2006 5:40 PM
To: Zaterka-Baxter, Kristin
Cc: Backstrom, Conra; Papile, Lu-Ann
Subject: Re: Fi02% adjustment for altitude

Kris, the information we have is below, our 2005 data compared to VON 2004. As you can see, we have more kids on O2 in every category, but send them home as soon or sooner (on O2). The left hand column - all babies - shows that we have the same number in hospital at 36 weeks, but more on O2; in the VLBW, fewer are in hospital, more on O2.

Let me know if this is helpful, and what questions you have. Kristi

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>>> "Zaterka-Baxter, Kristin" <kzaterka@rti.org> 6/22/2006 2:12 pm >>>
Hi,
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Thanks,
Kris

Kris Zaterka-Baxter
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4426 South Miami Blvd.
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Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 22, 2006 7:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; Das, Abhik; Petrie, Carolyn; Fernando Martinez; Wade Rich
Subject: Fi02% adjustment for altitude

Hi,
For the Support study, Dr Yoder (Utah) has suggested the following adjustment in Fi02% to determine what is considered in room air at high altitudes (5000 feet) based on barometric pressure. This will affect Utah and NM. Below is the suggested adjustment:

"Adjust all the FiO2 variables by a factor of 1.22 to account for the altitude at SLC compared to the other centers. Thus, "21%" at sea level is equivalent to 21*1.22 or 25.6% at 5000 feet. For ease of use we will assume that infants in < 25% FiO2 would be in room air at sea level."

Thanks,
Kris

From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Fi02% adjustment for altitude
Date: Tuesday, June 27, 2006 10:18:10 AM

Yes: with a couple of corrections Need to spell out SLC??? meaning unclear. Also why select an elevation of 5000 ft- there is probably a rationale, I'm just not familiar with what it is. We should put this in a technical memo and attach to the Phys Def protocol and manual.Michele

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: Michele Walsh
Sent: Monday, June 26, 2006 12:25 PM
Subject: FW: Fi02% adjustment for altitude

Michele
Is this ok with you?
Thanks
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 22, 2006 10:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: nfiner@ucsd.edu; Das, Abhik; Petrie, Carolyn; fmartinez@ucsd.edu; wrich@ucsd.edu
Subject: Fi02% adjustment for altitude

Hi,
For the Support study, Dr Yoder (Utah) has suggested the following adjustment in Fi02% to determine what is considered in room air at high altitudes (≥5000 feet) based on barometric pressure. This will affect Utah and NM. Below is the suggested adjustment:

"Adjust all the FiO2 variables by a factor of 1.22 to account for the altitude at SLC compared to the other centers. Thus, "21%" at sea level is equivalent to 21*1.22 or 25.6% at 5000 feet. For ease of use we will assume that infants in < 25% FiO2 would be in room air at sea level."

Thanks,
Kris

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: SUPPORT/UCSD
Date: Monday, June 26, 2006 5:57:16 PM

I will compose and send to you
Neilwr

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 26, 2006 9:10 AM
To: Neil Finer
Subject: RE: SUPPORT/UCSD

It is study specific – one paragraph would likely suffice that starts off "In the event of a recommendation of one arm being halted, the other arm could be continued with X, Y and Z being put into place for randomization, etc….." We would need to deal with a way to randomize which could be the same as we are doing now. The up side is that recruitment continues for that given arm. The downside is that if the halted arm resumes at some point in the future, we may not have the power to answer the question being asked for that particular arm. The other theoretical issue becomes funding - if the investigators desire to recruit the entire sample size in the "stopped and restarted" arm, additional dollars would be required.
Can we generate a paragraph for continuation of one arm and get the subcommittee first, then the steering committee to approve it?
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, June 26, 2006 1:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: SUPPORT/UCSD

HI Rose
I understand the recommendation of the DSMC – It would appear that the overall was stopped because we lacked a mechanism for stopping a single arm. I had previously raised the issue of the SAVE trial asking why both arms of that trial were stopped. I believe that that decision was not from the DSMC.
Let's work towards guidelines for stopping an arm. This does not appear to be a DSMC issue. My question is why did we not discuss stopping only the oximeter arm – my understanding was that we did not have a choice. How do we get such a procedure in place – would it be study specific, or is it a change to NICHD policy??
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 26, 2006 8:49 AM
To: Neil Finer
Cc: Wade Rich
Subject: RE: SUPPORT/UCSD

Neil
Look at the line above Dr. Alexander's recommendation: 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 need to have a procedure in place to continue one arm if the other is stopped – at the time, we did not have a mechanism in place to continue one arm.
We need to put one in place.
We are given the date of the DSMC meeting and NICHD now requires that the program scientist be available, if needed. If I have questions, I will call you (or Wally or other designee if you are not available). However, the DSMC recommends to the director, and this is done independently.

Thanks for your commitment to the trial!

Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, June 19, 2006 7:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: SUPPORT/UCSD

Hi Rose
I will discuss the arrangements with my Department. For now I will continue.
I would like to have either myself or another member of the Steering Committee – Wally, on standby if there is a DSMC meeting. You could then call us if there are any questions.
My understanding of the results of the DSMC meeting last November was the Dr Alexander paused the entire trial. We did not have the option of continued enrollment or at least that option was not presented to me or the Subcommittee. Thje exact wording was as follows:
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.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 19, 2006 1:04 PM
To: Neil Finer
Subject: SUPPORT/UCSD

Neil
You have asked several questions regarding your site and SUPPORT – to answer the questions, I offer the following

1. Salary support for Wade and yourself – I have been informed that this is not possible form the NICHD NRN budget.
2. If lack of salary support precludes involvement in the SUPPORT protocol, we would need to name another PI. Your expertise and involvement in the project has been key to development, initiation

and resumption of the trial. If UCSD will not allow you to participate without salary support, we would understand, though I feel it would be a major loss to the study.

3. It is possible and advantageous to continue one arm of the SUPPORT trial if one arm is halted. We would simply continue randomization in the other arm. I will discuss the mechanism to do this with the data center. If you note, the letter last time halted the oximetry arm.
4. DSMC meetings – I have explored this issue – Each institute at NIH establishes their policies for the oversight of trials. NICHD does not have investigator involvement with the DSMC unless requested by the DSMC. The program scientist is available at the time of the meeting, but only would join at the request of the DSMC.

Let me know if there are other questions

Thanks for all your commitment!
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: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Miami follow up patients
Date: Monday, June 26, 2006 9:55:20 AM

Thanks
Shahnaz

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 26, 2006 9:53 AM
To: Duara, Shahnaz
Subject: RE: Miami follow up patients

As of March 22, 2006, Ken had told me that the Miami site had 128 children discharged alive and 15 Support infants discharged alive for FU.
Capitations are as follows:
GDB $96
Candida $484 + $100 patient care
EOS $96
BPD/Physio def $64
SUPPORT RCT $2000/pt enrolled
SUPPORT MRI $1314
SUPPORT BREATHING OUTCOMES $224
SUPPORT Growth To Be determined
SUPPORT Antenatal To be determined
Follow-up $300 for <1000g, extra $150 if in another study

Let me know if you need anything else.
Rose

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Tuesday, June 20, 2006 3:59 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Miami follow up patients

Hi Rose,

Sorry to be a bother, but I know that prior to the calls we had at the end of March, Ken had put together a list of babies due to be seen at follow up in Miami over the 24 months starting 4/1/06. I am putting together our budget and would like to have those numbers - if I got them, I've misplaced the list. Also, if you could send me the current rate per GDB baby and the rate per protocol baby, it will help me to draft an accurate budget.

Thanks
Shahnaz

From: Neil Finer
To: Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Petrie, Carolyn; Fernando Martinez; Wade Rich
Subject: RE: Fi02% adjustment for altitude
Date: Thursday, June 22, 2006 1:36:24 PM

Hello Everyone

I think that this is OK if all of their data is sent to RTI, and any correction is applied by RTI. Thus, we would want to know the actual FiO2, even if the infant is not considered to be on SUPPORT. One issue here is do infants at altitude on 25% experience the same high SpO2 that infants at sea level experience in room air.

Perhaps we should also ask Brad or Roger if they have the data. If not, the only way we will ever get this information is to continue the study oximeter till these infants are off oxygen or at 36 weeks. This may require more oximeters for these centers. What percent of the infants at these 2 units are on oxygen at 36 weeks?

Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 22, 2006 7:59 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; Das, Abhik; Petrie, Carolyn; Fernando Martinez; Wade Rich
Subject: Fi02% adjustment for altitude

Hi,
For the Support study, Dr Yoder (Utah) has suggested the following adjustment in Fi02% to determine what is considered in room air at high altitudes (≥5000 feet) based on barometric pressure. This will affect Utah and NM. Below is the suggested adjustment:

"Adjust all the FiO2 variables by a factor of 1.22 to account for the altitude at SLC compared to the other centers. Thus, "21%" at sea level is equivalent to 21*1.22 or 25.6% at 5000 feet. For ease of use we will assume that infants in < 25% FiO2 would be in room air at sea level."

Thanks,
Kris

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT BABY
Date: Tuesday, June 20, 2006 9:35:59 AM

Rose:

I just called you, but now realize that you are out. I do tend to agree with Neil. Since the entry criteria were wrongly estimated in the beginning, this subject should not be in the study. To me, intent-to-treat applies for all eligible subjects who are randomized, and this subject clearly was not eligible.

I also wanted to talk to you about another issue. The NEC call yesterday, and the resulting decision to take this to the steering committee, though understandable, somewhat bothers me a bit. It seems to undermine (or, at least, gives that impression) the Network's rigorous protocol review process when a proposal that has received less-than-enthusiastic reviews twice from the PRS then goes over its head to appeal directly to the SC, which, as Jon himself said, wont really have a chance to intelligently and exhaustively review its merits. I don't expect a response from you on this; just something to think about.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 19, 2006 5:43 PM
To: Das, Abhik
Subject: Fw: SUPPORT BABY

Do you agree?

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org <adas@rti.org>; Nancy Miller <Nancy.Miller@UTSouthwestern.edu>
Sent: Mon Jun 19 16:44:42 2006
Subject: RE: SUPPORT BABY

Hi Rose

I believe that this infant should be excluded as the gestational age is an exclusion and the randomization was done pending the infant qualifying. Including the infant would be problematic because of the gestational assessment and the lack of resuscitation which is another exclusion # 3.2 - physician decision to forego resuscitation.

I would not include as intention to treat because of both of these.

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 19, 2006 12:33 PM
To: Neil Finer
Cc: adas@rti.org; Nancy Miller
Subject: SUPPORT BABY

HI

Dallas had an infant deemed to be 24 3/7th weeks by best OB assessment. The infant was randomized prior to delivery. At delivery, the infant was felt to be about 22 weeks estimated gestational age, so resuscitation was not initiated. Since this is an intent to treat study, I think this baby should be included. After delivery, the baby did meet an exclusion criteria of < 24 weeks, but we based the study on "best ob assessment."

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

Prior to delivery, the infant met all of the above criteria.

After delivery, the baby did meet an exclusion criteria of < 24 weeks, but we based the study on "best ob assessment."

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

What are your thoughts?
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: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Walid Salhab
Subject: Re: Pulse Oximeters for SUPPORT
Date: Monday, June 19, 2006 4:12:14 PM

Rose,
Walid would like your opinion on how many extra pulse ox's we should request. We have two singletons and a set of(b) (6) consented for SUPPORT. We have 4 orange pulse ox's and 3 blue.
Thank you,
Nancy

Nancy A. Miller, R.N.
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-502
Dallas, Texas 75390-9063
214-648-3780
pager 972-206(b) (6)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Monday, June 19, 2006 11:55:56 AM

If they are available great – if not I do not think that will be a problem.
We can cover at a later call
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, June 19, 2006 6:44 AM
To: Neil Finer
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Neil
As I looked over the agenda, I realized that we don't have any of the PI's for the secondary studies (Hintz, Stevens, Navarrete). It may be a little late to get them on the call today – do you want me to try or should we do a separate call? Susan Hintz and I are I the process of repelling the sites as to participation on MRI.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Sunday, June 18, 2006 7:29 PM
To: Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) [redacted]; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Please find attached an Agenda for tomorrows Teleconference.
Please bring any additional items to the call
Be well
Talk to you tomorrow.
Neil

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, June 16, 2006 12:33 PM
To: Petrie, Carolyn; Neil Finer; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; (b) (6) [redacted]; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject: RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET

Reminder for Monday's call

The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19
12:00-1:00pm ET

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

Agenda
Trial Progress
New Site Orientation
Recruitment
SUPP05 Form - Newman
New business

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

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To:	Petrie, Carolyn; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; Wade Rich; Gantz, Marie
Cc:	Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; Fernando Martinez; bvecchio@careNE.org; Webb, Robin E.
Subject:	RE: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date:	Sunday, June 18, 2006 7:29:13 PM
Attachments:	Agenda for SUPPORT Subcommittee Teleconf June 19 06.doc

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Agenda for SUPPORT Subcommittee Meeting – June 19 2006

1. Review Enrollments to date –about 290.

Leading enroller is Case Western, followed by UT Texas, Brown and Emory
Three active ongoing centers have < 5 enrollments from the beginning of the trial, Stanford, Wayne State and Yale
19 enrollments in April, 10 in May.
Our target should be 3 per center per month – 36/center/year. If we can achieve this rate we would enroll 570/year and be complete within a little over 2 years
At 2/month/center - we would enroll 384/year and we would be completed in 3 years from now.
I would like to see this trial be complete in 3 years.
The COIN trial has completed enrollment. SUPPORT and VON trials are ongoing. Ours is the only trial to include infants of 24 weeks, Coin has 25 wks and VON 26 weeks. Ours is the first to look at Oximeter ranges and we are leading the world here.
Please bring any suggestions to the conference call to stimulate recruitment.

2. New Centers – Site visits being considered. Abbot to go to Boston. I will do Salt Lake and Albuquerque. Anyone for Iowa??
3. Secondaries – MRI – Use of Hugger.
    a. Ability to get consents
    b. MRI time
    c. Other issues

4. Breathing Outcomes – Rochester or site doing the interviews?

Have all centers chosen and any issues.

4. Trial Issues – We modified Supp05 at request of coordinators. The resultant new forms were sent out for approval and we did not have any responses. This was discussed at the last coordinator call. Our real interest in the changes was to have FiO2 q2h for assessing oximeter data in the first 14 days, and allowing us to know if the infant is on oxygen or room air. On room air there is a significantly greater % of time with SpO2 > 96%, and we need to know this to determine if we are staying in target while on oxygen.

We do not have any additional oximeters data for circulation at the present as Marie is redoing the software. We may have more information by the time of the Steering Committee.
For multiples consented and randomized but only 1 delivers, the others may be enrolled if they deliver in the window.

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondry
Date: Friday, June 16, 2006 12:51:02 PM

Well, know that she has looked at the actual tables in the monthly report and commented on them, we can work with her on the changes. Just wanted you to know the history!

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 16, 2006 12:16 PM
To: Das, Abhik
Subject: RE: SUPPORT secondry

Send me the shell tables and I can send them out – sometimes the response is better!
Thanks
Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Friday, June 16, 2006 12:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT secondry

Rose:

We are happy to work with Susan in refining the monthly report table so that it works best for her. Just as an FYI, Kris sent her the table shells in May asking for her feedback and suggestions before this went on the monthly report, but never heard back!

Thanks

Abhik

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, June 16, 2006 11:35 AM
To: higginsr@mail.nih.gov
Cc: Das, Abhik
Subject: SUPPORT secondry

Hi Rose,

I am concerned about the SUPPORT secondary MRI enrollment numbers. It looks like only the UCSD patients that were enrolled oh so long ago are showing up in the RTI output. I know that we embed in our consent for the MRI WITH the main trial consent, and that is supposedly true for Houston and Case based on their responses to previous email queries.

Part of this may be a problem with the re-opening of the trial. Part of this may be an issue of tracking/forms completion. There IS a form that should be completed for the secondary

enrollment (form MRI 01) and perhaps there needs to be an edit generated for whether that form is missing among sites that have indicated their plans to participate in the secondary. Clearly we at Stanford are guilty of some problem in this regard because all of our SUPPORT patients have been enrolled in the MRI secondary (although our total number of SUPPORT patients are not many I'm afraid).

My thoughts are the following:

1) I think I need to send out ANOTHER email questionnaire to the OLD sites. I will individually query those that have indicated they are intending to participate with respect to where we left off - i.e., have they gotten their IRB approval for the secondary yet, have they enrolled their first MRI patient, etc. As of the last round of emails for updates in March, a few of the old sites still had not really responded definitively about their participation.

2) Send another email to the NEW sites - The last round of queries did not yield much, but they were just starting up then. By now they should be able to respond fully.

3) I need to work with RTI to put together a more complete report page for the MRI secondary. I think it would be helpful to see at least the following information on a report page: 1) all the sites listed that have indicated their intention to participate (even if they "formally" have no MRI secondary patients), 2) the # of SUPPORT patients enrolled since their receipt of MRI secondary IRB approval, 3) the # of patients with completed enrollment forms for the MRI secondary, 4) number of MRIs and cranial US from the site received by RTI. This way, we can more easily identify whether certain sites are simply NOT enrolling in the MRI secondary, or whether the MRI 01 is simply missing but indeed a patient has been enrolled. Thus, as I mentioned above, perhaps an edit would be useful.

Do these steps sound resonable to you? I will proceed with drafting some emails. Maybe we can get them sent out next week. Also Abhik, I will communicate with you further about the report page - I would be very happy to have your advice on further useful information to be included.

Thanks

Susan

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: adas@rti.org
Subject: RE: SUPPORT secondry
Date: Friday, June 16, 2006 12:37:12 PM
Attachments: oldsitesSUPPORTsecondary032306.xls
newsitesSUPPORTsecondary032906.xls

Rose

You mean the emails? I agree that the email questions/reminders to sites are better and more effective coming from you. I will send them to you as soon as I have them drafted.

I am attaching the latest spreadsheets with responses from the sites - but I will work on drafting the emails because you shouldn't have to do that! I will also work with RTI to change the report page and see if an edit can be worked into the process.

Thanks

Susan

> Susan
>
> I will have Kris send me the tables - and I can send them out - sometimes the response is better.
>
> I think the fourth suggestion is fine - work with RTI.
>
> Thanks
>
> Rose

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, June 16, 2006 11:35 AM
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Cc: adas@rti.org
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Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi
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

SITES	1. Has your site received IRB approval for the SUPPORT Neuroimaging secondary? **YES/NO**	2. Will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall study consent? **Separate/Embedded**	3.If your site has not received IRB approval, has your site applied for IRB approval for the SUPPORT Neuroimaging secondary?	If not, does your site intend to participate	Approval	Date of latest update
Alabama	Yes	unanswered	N/A	N/A	**Approved**	
Case	No	Embedded	We did but was returned - I will resubmit with a separate consent	Yes	Pending	
Dallas	Yes	Separate	N/A	N/A	**11/4/2005**	3/23/2005
Wayne						
Miami				No		
Emory						
CinA						See comment
CinB						
CinC						
Indiana	No	Separate	Once we can get the SUPPORT main study re-opened with our IRB, I'll be submitting this for review/approval.	Yes	Pending	
Yale						
Brown	Yes	Separate	N/A	N/A	**Approved 12/19/05**	
Stanford	Yes	Embedded	N/A	N/A	**Approved 09/27/05**	
Houston	Yes	Embedded	N/A	N/A	**Approval 10/25/05**	revised, see comment 03/23/06
Duke	Pending	Separate	Yes, submission is at the IRB	N/A	Pending	3/23/2006
WF (1) Bowman Gray						
WF (2) Forsyth				No		

Roch	Yes	Embedded	N/A	N/A	Approved 12/2005	
UCSD#1	Yes	Separate	N/A	N/A	Approved 08/18/05	
UCSD#2						

Site	Date Reported	1. Is IRB approval pending for the SUPPORT Neuroimaging secondary at your site?	If pending will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall SUPPORT consent?	2. If IRB approval is not pending at your site, does your site intend to participate in the SUPPORT Neuroimaging secondary?	3. If your site does not intend to participate, what were the main limitations for participation?
23	3/28/2006	No	N/A	Pending further review of the study. Currently focusing on IRB approval for other NRN studies	N/A
24					
25					
26					

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh; Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Wade Rich; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF)
Subject: RE: Support revisions
Date: Thursday, June 15, 2006 11:30:21 AM

Rose
We should include the new members of the committee in any future communications. Would you please forward this to them – I think Abbot and Brad Yoder. Have I missed anyone?
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 15, 2006 7:24 AM
To: Michele Walsh; Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Wade Rich; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF); Neil Finer
Subject: RE: Support revisions

Kris had sent an email with the preliminary changes and requests for suggestions by June 9. NO substantive suggestions were made and no suggestions for a discussion by the subcommittee were requested.

Thanks
Rose

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, June 15, 2006 10:45 AM
To: Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Rich, Wade; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF); Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support revisions

Hi All: I am suprised that this many changes would have been made without the SUPPORT Investigators subcommittee having discussion ahead of time. While most likely
the changes would have been approved, this is substantially different than the process in other Network studies. Could you give me some background? Did I miss an email vote on the changes? Talk to you on Monday.
Regards, Michele

> ----- Original Message -----
> **From:** Zaterka-Baxter, Kristin
> **To:** Pablo.Sanchez@UTSouthwestern.edu ; Nancy.Miller@UTSouthwestern.edu ; sshankar@med.wayne.edu ; ae5357@wayne.edu ; [SCRN] Stoll, Barbara ; ellen_hale@oz.ped.emory.edu ; grisbyca@email.uc.edu ; bpoindex@iupui.edu ; lucmille@iupui.edu ; richard.ehrenkranz@yale.edu ; monica.konstantino@yale.edu ; Angelita Hensman ; dstevenson@stanford.edu ; mbball@leland.stanford.edu ; mcollins@peds.uab.edu ; jon.e.tyson@uth.tmc.edu ; Georgia E McDavid ; goldb008@mc.duke.edu ; auten002@mc.duke.edu ; Frantz, Ivan ; Furey, Anne ; Bell, Edward ; Johnson, Karen ; Susan Tepper ; Kristi Watterberg ; Conra Backstrom
> **Cc:** wcarlo@peds.uab.edu ; mcw3@cwru.edu ; bradley.yoder@hsc.utah.edu ; Roger.faix@hsc.utah.edu ; alaptook@WIHRI.org ; kurt.schibler@cchmc.org ; Nancy Newman ; Wade Rich ; Gantz, Marie ; Higgins, Rosemary (NIH/NICHD) [E] ; Das, Abhik ; Petrie, Carolyn ; Auman, Jeanette O. ; Schaefer, Scott E. ; Pickett, James ; Price, Jeffrey M.
> **Sent:** Tuesday, June 13, 2006 8:55 PM
> **Subject:** Support revisions

Hello everyone,

We've made a few revisions to the Support manual and two study forms. These revisions were primarily based on discussions during the last coordinators conference call. Please note that changes made to Chapter 10 and form SUPP05a were prompted by RTI so that we can program the data entry system to allow cleaner data to be obtained for analysis. Please find attached a technical memo outlining these revisions and the revised manual (highlighted and clean copy) and forms. Please let me know if there are any questions. The revised documents will be posted on the NRN web shortly.

Thanks as always,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support revisions
Date: Thursday, June 15, 2006 11:29:38 AM

Hi,
Do the GDB revisions re. the race and ethnic categories need to go to the GDB Subcommittee? Likewise, do the EOS revisions reflecting the same changes in addition to the new chapter explaining the new EOS survey to capture all live births annually need to go to the EOS subcommittee. Dr. Stoll approved these changes a couple of weeks ago
Thanks
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 15, 2006 11:24 AM
To: Michele Walsh; Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Rich, Wade; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF); Finer, Neil
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To: Pablo.Sanchez@UTSouthwestern.edu ; Nancy.Miller@UTSouthwestern.edu ; sshankar@med.wayne.edu ; ae5357@wayne.edu ; [SCRN] Stoll, Barbara ; ellen_hale@oz.ped.emory.edu ; grisbyca@email.uc.edu ; bpoindex@iupui.edu ; lucmille@iupui.edu ; richard.ehrenkranz@yale.edu ; monica.konstantino@yale.edu ; Angelita Hensman ; dstevenson@stanford.edu ; mbball@leland.stanford.edu ; mcollins@peds.uab.edu ; jon.e.tyson@uth.tmc.edu ; Georgia E McDavid ; goldb008@mc.duke.edu ; auten002@mc.duke.edu ; Frantz, Ivan ; Furey, Anne ; Bell, Edward ; Johnson, Karen ; Susan Tepper ; Kristi Watterberg ; Conra Backstrom
Cc: wcarlo@peds.uab.edu ; mcw3@cwru.edu ; bradley.yoder@hsc.utah.edu ; Roger.faix@hsc.utah.edu ; alaptook@WIHRI.org ; kurt.schibler@cchmc.org ; Nancy Newman ; Wade Rich ; Gantz, Marie ; Higgins, Rosemary (NIH/NICHD) [E] ; Das, Abhik ; Petrie, Carolyn ; Auman, Jeanette O. ; Schaefer, Scott E. ; Pickett, James ; Price, Jeffrey M.

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Thanks as always,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Neil Finer
To: Michele Walsh; Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Wade Rich; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF); Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject: RE: Support revisions
Date: Thursday, June 15, 2006 11:26:40 AM

Hi Michele
These changes were prompted by concerns that the coordinators had about data entry, especially regarding days on oxygen and times. There were no changes in protocol. We didn't feel that we needed a separate discussion as I assumed that the individual coordinators were discussing with there PIs. If that is not the case, and there are concerns, we should discuss.
We have a teleconference scheduled for next Monday and we made that as early as we could according to everyone's schedule. We can review or discuss these changes then if you wish.
Neil

From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, June 15, 2006 6:45 AM
To: Zaterka-Baxter, Kristin
Cc: Newman, Nancy; Wade Rich; Duara, Shahnaz; Carlo, Wally; Donovan, Edward (DONOVAEF); Neil Finer; Higgins, Rose
Subject: Re: Support revisions

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----- Original Message -----
From: Zaterka-Baxter, Kristin
To: Pablo.Sanchez@UTSouthwestern.edu ; Nancy.Miller@UTSouthwestern.edu ; sshankar@med.wayne.edu ; ae5357@wayne.edu ; [SCRN] Stoll, Barbara ; ellen_hale@oz.ped.emory.edu ; grisbyca@email.uc.edu ; bpoindex@iupui.edu ; lucmille@iupui.edu ; richard.ehrenkranz@yale.edu ; monica.konstantino@yale.edu ; Angelita Hensman ; dstevenson@stanford.edu ; mbball@leland.stanford.edu ; mcollins@peds.uab.edu ; jon.e.tyson@uth.tmc.edu ; Georgia E McDavid ; goldb008@mc.duke.edu ; auten002@mc.duke.edu ; Frantz, Ivan ; Furey, Anne ; Bell, Edward ; Johnson, Karen ; Susan Tepper ; Kristi Watterberg ; Conra Backstrom
Cc: wcarlo@peds.uab.edu ; mcw3@cwru.edu ; bradley.yoder@hsc.utah.edu ; Roger.faix@hsc.utah.edu ; alaptook@WIHRI.org ; kurt.schibler@cchmc.org ; Nancy Newman ; Wade Rich ; Gantz, Marie ; Higgins, Rosemary (NIH/NICHD) [E] ; Das, Abhik ; Petrie, Carolyn ; Auman, Jeanette O. ; Schaefer, Scott E. ; Pickett, James ; Price, Jeffrey M.
Sent: Tuesday, June 13, 2006 8:55 PM
Subject: Support revisions

Hello everyone,

We've made a few revisions to the Support manual and two study forms. These revisions were primarily based on discussions during the last coordinators conference call. Please note that changes made to Chapter 10 and form SUPP05a were prompted by RTI so that we can program the data entry system to allow cleaner data to be obtained for analysis. Please find attached a technical memo outlining these revisions and the revised manual (highlighted and clean copy) and forms. Please let me know if there are any questions. The revised documents will be posted on the NRN web shortly.

Thanks as always,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
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From:	Zaterka-Baxter, Kristin
To:	Pablo.Sanchez@UTSouthwestern.edu; Nancy.Miller@UTSouthwestern.edu; sshankar@med.wayne.edu; ae5357@wayne.edu; [SCRN] Stoll, Barbara; ellen_hale@oz.ped.emory.edu; grisbyca@email.uc.edu; bpoindex@iupui.edu; lucmille@iupui.edu; richard.ehrenkranz@yale.edu; monica.konstantino@yale.edu; Angelita Hensman; dstevenson@stanford.edu; mbball@leland.stanford.edu; mcollins@peds.uab.edu; jon.e.tyson@uth.tmc.edu; Georgia E McDavid; goldb008@mc.duke.edu; auten002@mc.duke.edu; Frantz, Ivan; Furey, Anne; Bell, Edward; Johnson, Karen; Susan Tepper; Kristi Watterberg; Conra Backstrom
Cc:	wcarlo@peds.uab.edu; mcw3@cwru.edu; bradley.yoder@hsc.utah.edu; Roger.faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Nancy Newman; Wade Rich; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Petrie, Carolyn; Auman, Jeanette O.; Schaefer, Scott E.; Pickett, James; Price, Jeffrey M.
Subject:	Support revisions
Date:	Tuesday, June 13, 2006 8:55:54 PM
Attachments:	SUP09.doc SUPPORT_Manual[Updated06.05.06 uc].doc SUPPORT_Manual[Updated06.05.06 cc].doc SUPP05ASafetyMonitor[06.05.06 v2.1(cc)]Rev.doc SUPP11[Rev 06.05.06 cc] .doc

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RTI INTERNATIONAL | **Memorandum**

June 5, 2006

SUPPORT TECHNICAL MEMO # 9

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Clarifications to the Manual of Procedures/Forms

The following items have been clarified in the Manual of Procedures and Forms SUPP11 and SUPP05a:

Chapter 2
The 4 new NRN centers have been added to the manual on page 2.2, section 2.3 Participating NICHD Neonatal Research Network Centers.

The Support Subcommittee has been updated in the manual on page 2.1, section 2.2 SUPPORT Trial Subcommittee

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Chapter 5
Clarification was requested during the April 2006 coordinators conference call regarding manual guidelines for extubation after re-intubation for the control (surfactant) arm. The following underlined text has been added to page 5-4, section 5.1.8 (3) Reintubation:

Control Infants may be reintubated using Standard of Care. Any subsequent extubation will also follow standard practice.

Chapter 10 (Section 10.2.2, page 10-3)
When programming the revision to form SUPP05a per the March 7, 2006 technical memo, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report. Therefore, we have deleted Section C as suggested in March and modified this forms to allow each event to be reported separately.

Please note that this version supersedes the revision in March which was not programmed. This version requests the same data as the previous version dated 10/03/2005 with the addition of a date and time for each event:

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

ADDED: **Report Number**

Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day

Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date

Record the date in which the intubation/extubation occurred.

Section B

Section 10.2.3 (Section C) has been deleted.

***Form SUPP05a** has been revised to reflect this revision (version 2.1; dated 06/05/06).*

Chapter 16

A request was made during the May 2006 coordinators conference call to add a code identifying infants who are in no support all day and off the study oximeter for any days between day 15 through 36 weeks. The following underlined text has been added to page 16-1, section 16.1.1 (bullet 3):

Highest Level of Support
Record the highest level of support the infant is in at the scheduled time points during this STUDY day.
Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
7= No Support, 9= No Support all day and off the study oximeter*.

* Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

***Form Supp11** has been modified to include Code 9 (version 2.1; dated 06/05/06).*

The updated Manual of Procedures and forms SUPP05a and SUPP11 have been posted on the Neonatal Web site with the revision date of 06/05/06.

cc: Rosemary Higgins

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006

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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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~~ Bradley Yoder, MD; Roger Faix, MD

Michele Walsh, MD

~~Shahnaz Duara, MD~~ Abbot Laptook, MD

Kurt Schibler, MD

Rosemary D. Higgins, MD

~~W. Kenneth Poole, PhD~~ Abhik Das, PhD

~~Ruth Everett, RN~~ Nancy Newman, RN

Wade Rich, RRT

Marie Gantz, PhD

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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. **Any subsequent extubations will also follow standard practice.**

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 <u>No</u> 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. $pC0_2$:

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 $Sa0_2$ ≥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
SUPP05 and SUPP05A

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

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 results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**

Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured
For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. 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.

For all other time points enter the FiO_2 and Mode of Support.

c. pH
Record the acid base status of the blood.
d. $C0_2$
e. PO_2:
f. FiO_2
Record the **FiO_2** at the time the blood gas was collected or at other scheduled time points.
g. Source:
Record the source of the blood gas
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

i. If Mode =5 record Flow Rate
Record the flow rate for infants on nasal cannula

4. If Mode of Support =4 (CPAP), type used:
Record the type of CPAP
2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

13. Oximeter Alarm Check.
The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine.

The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

14. 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

15. Was the infant intubated or extubated on this day?
If Yes, Complete Section B and/or Section C of the SUPP05A

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

Section B

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 information prior to intubation:
Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record ""*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code ""*
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
4. Saturation

~~**10.2.3 Section C. Intubation/Extubation Information (For NICU ONLY)**~~
~~**If more than one intubation/extubation occurs in one day, complete Section C.**~~
~~Record the intubation/extubation history for each Study Day 1–14.~~
~~**1. Did the infant have more than one intubation/extubation on this day?**~~
~~**If Yes,**~~
~~**2. 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 information prior to intubation:**~~
~~***Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record "*"***~~
~~***Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code "*"***~~
~~**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 thisday.~~

~~**9. Other (specify).** Record Yes if the infant had other conditions this day. **Specify these.**~~

~~**3. 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**~~

~~**4. Saturation**~~

~~***NOTE: If more than two intubations/extubations were performed, complete additional SUPP05A, Section C for this study day.***~~

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 Kris Zaterka-Baxter 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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, **9= No Support all day and off the study oximeter***.

  *** Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.**

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b) [redacted]

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

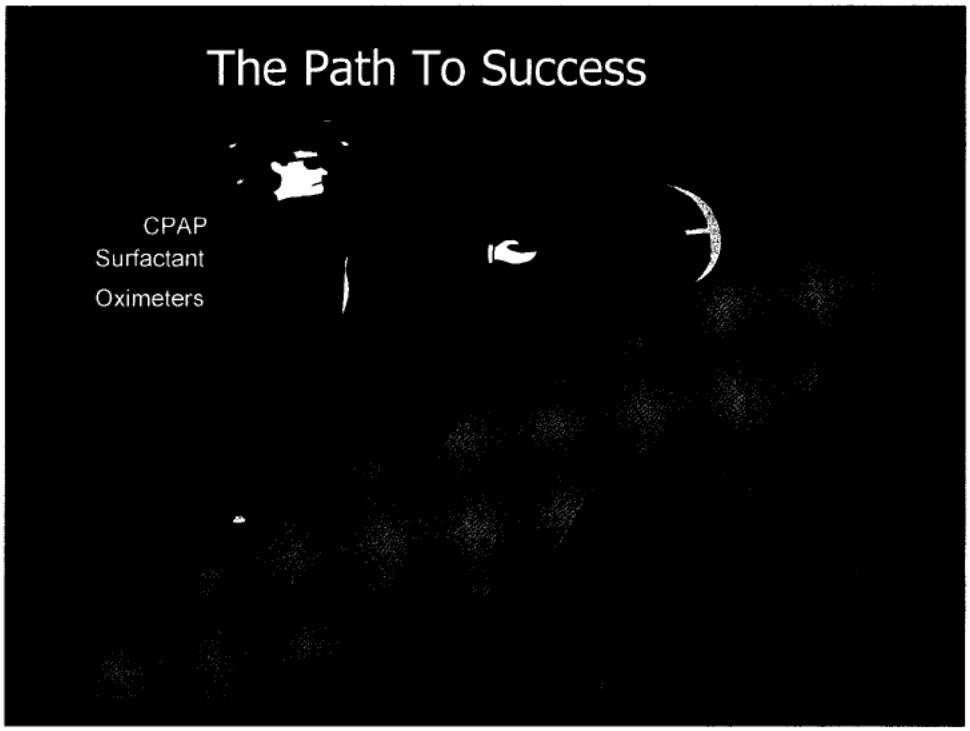
Signature of person explaining and getting consent DATE

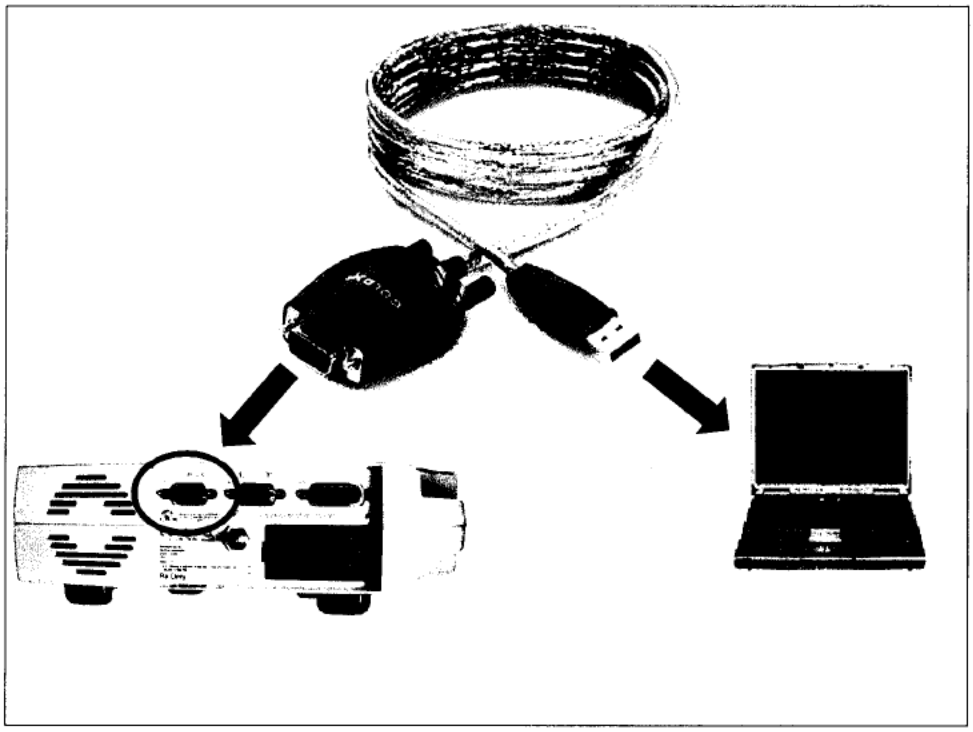
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

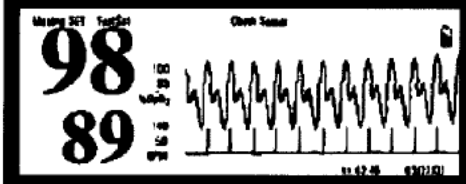
Use arrow key to select "Binary".

Select button.

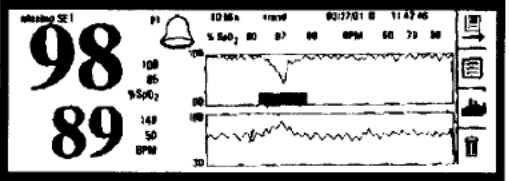
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

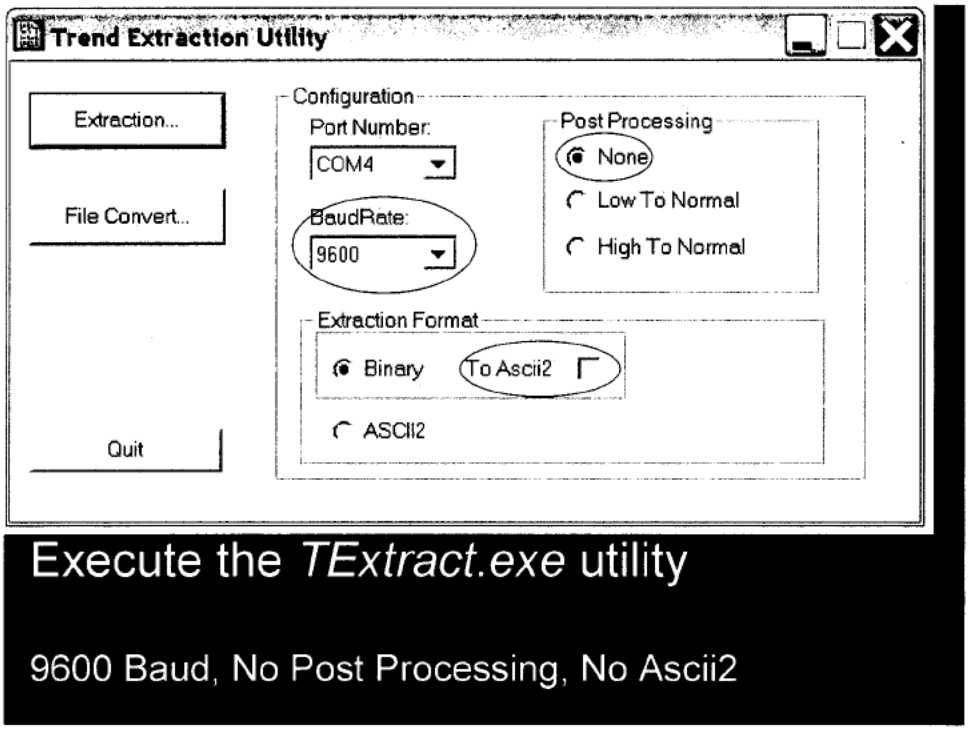
Make sure the Radical is in run mode and not in mode.



YES

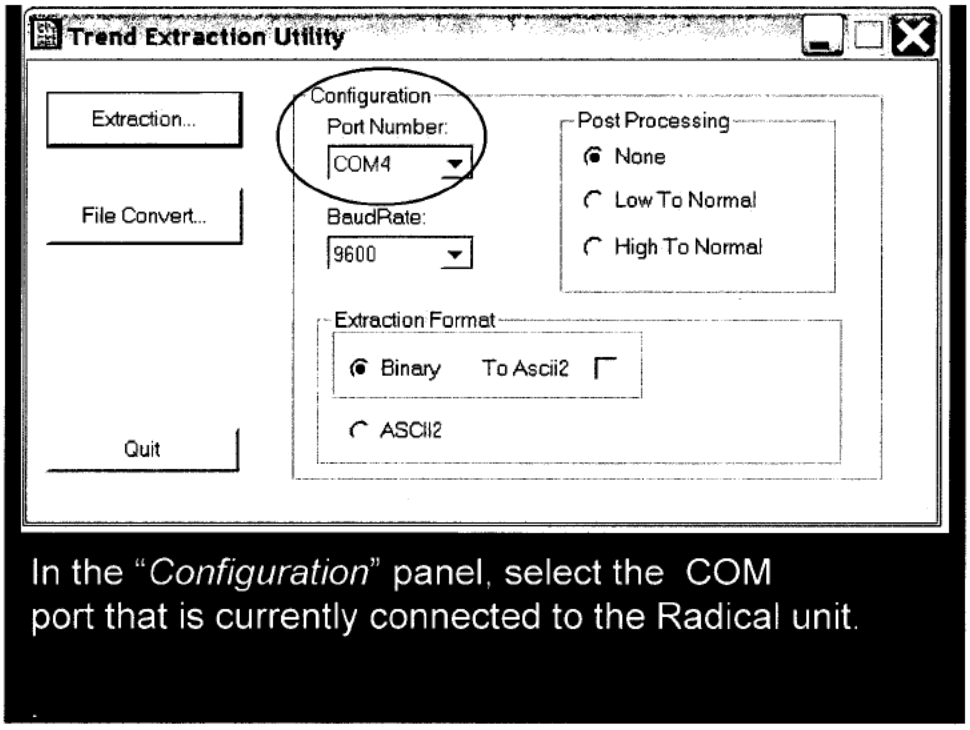


No

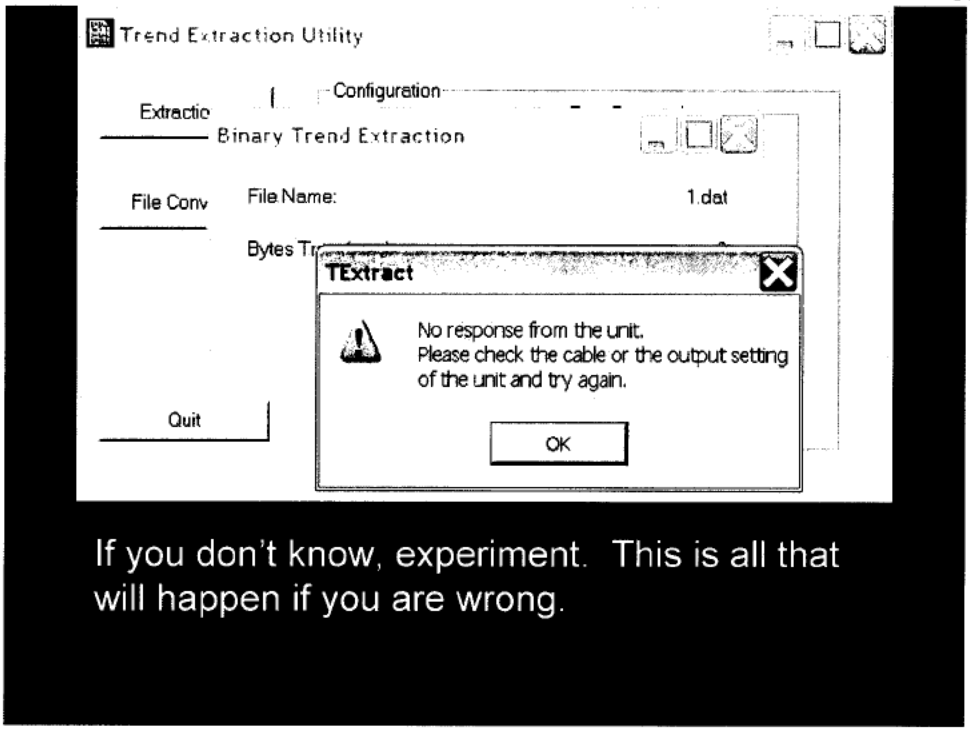


Execute the *TExtract.exe* utility

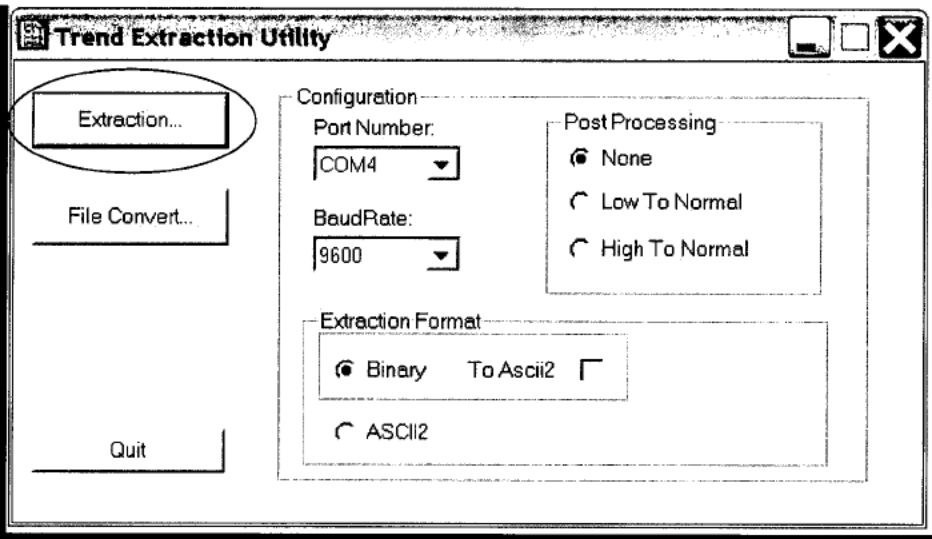
9600 Baud, No Post Processing, No Ascii2



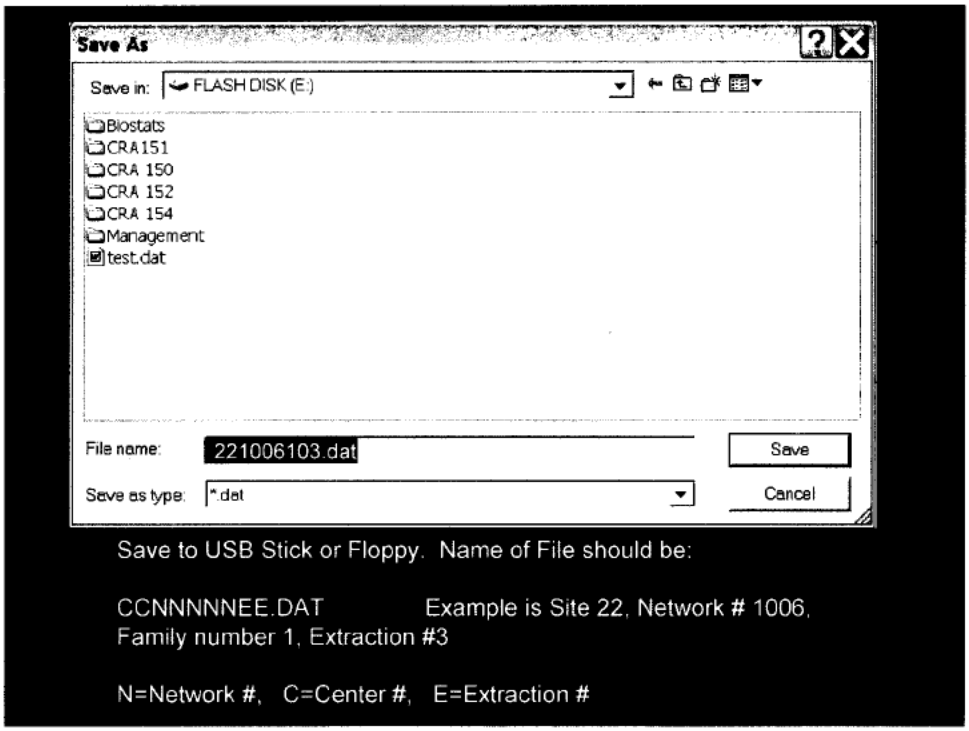
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

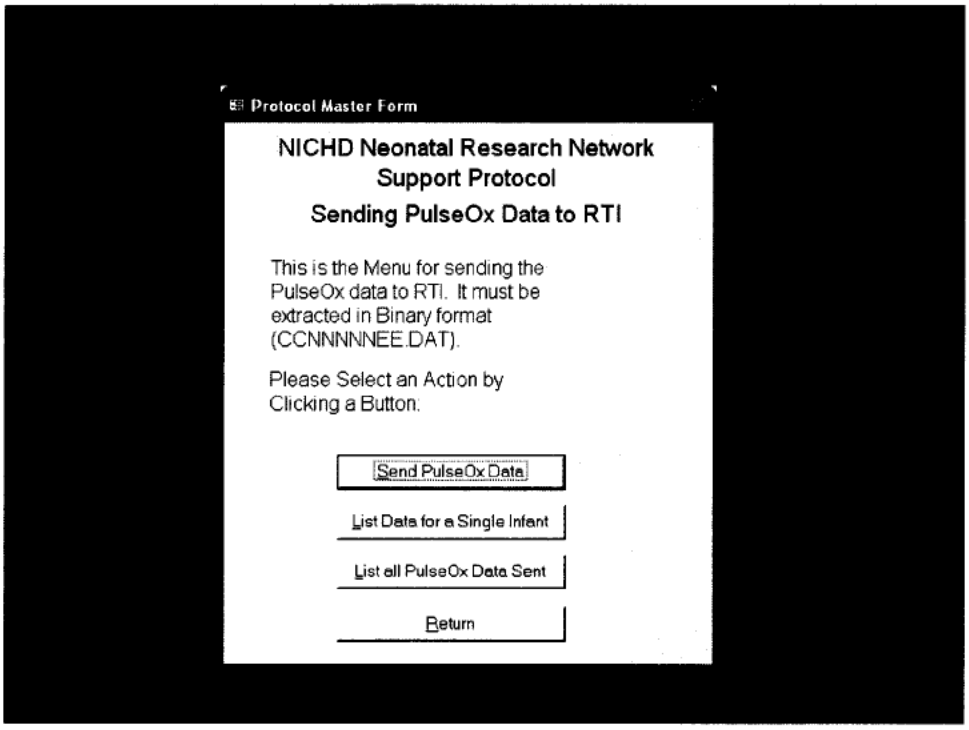


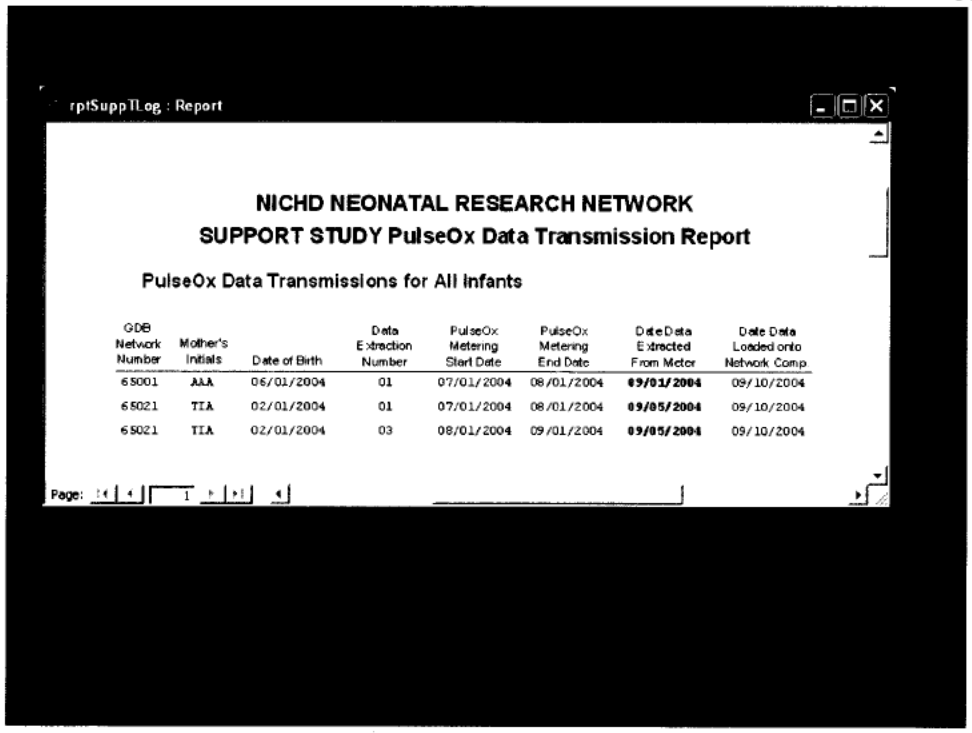
If you don't know, experiment. This is all that will happen if you are wrong.

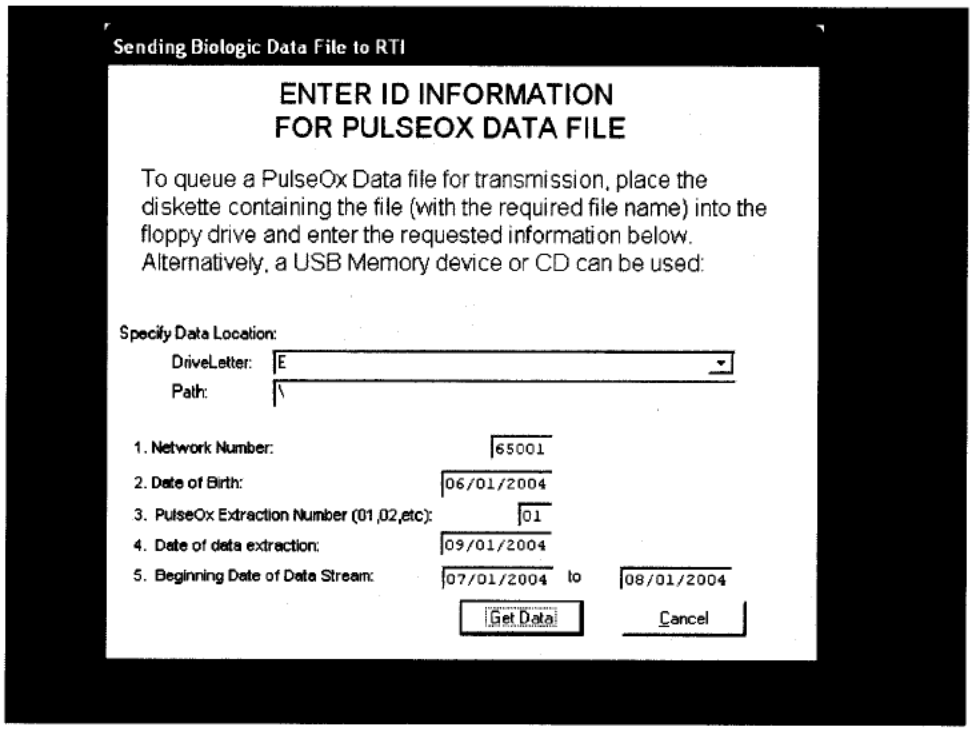


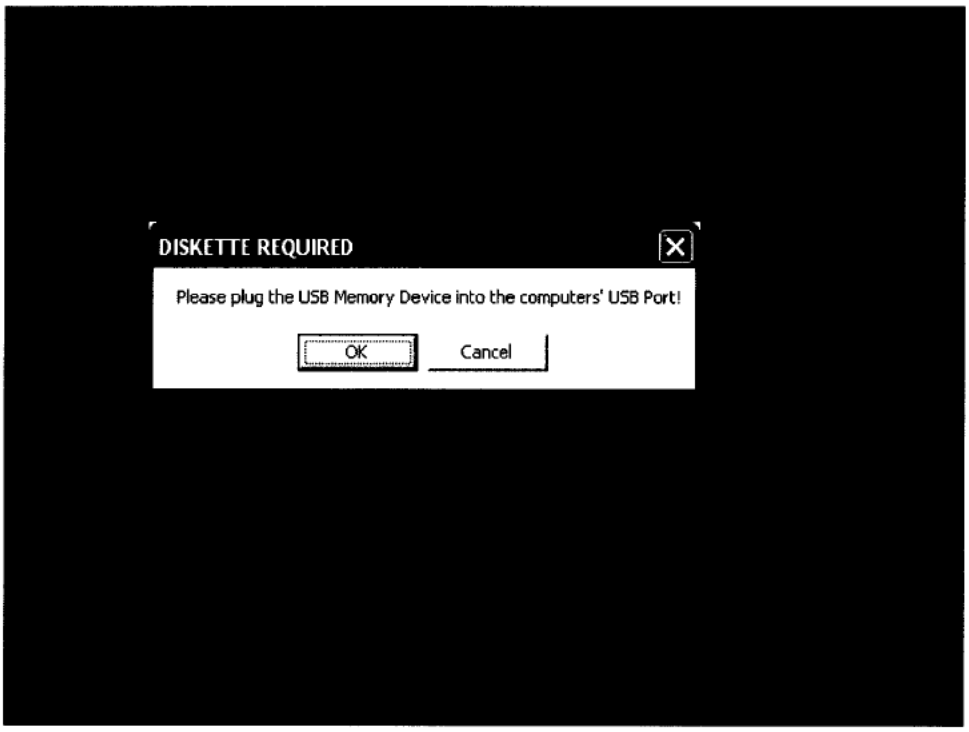
Hit Extraction.

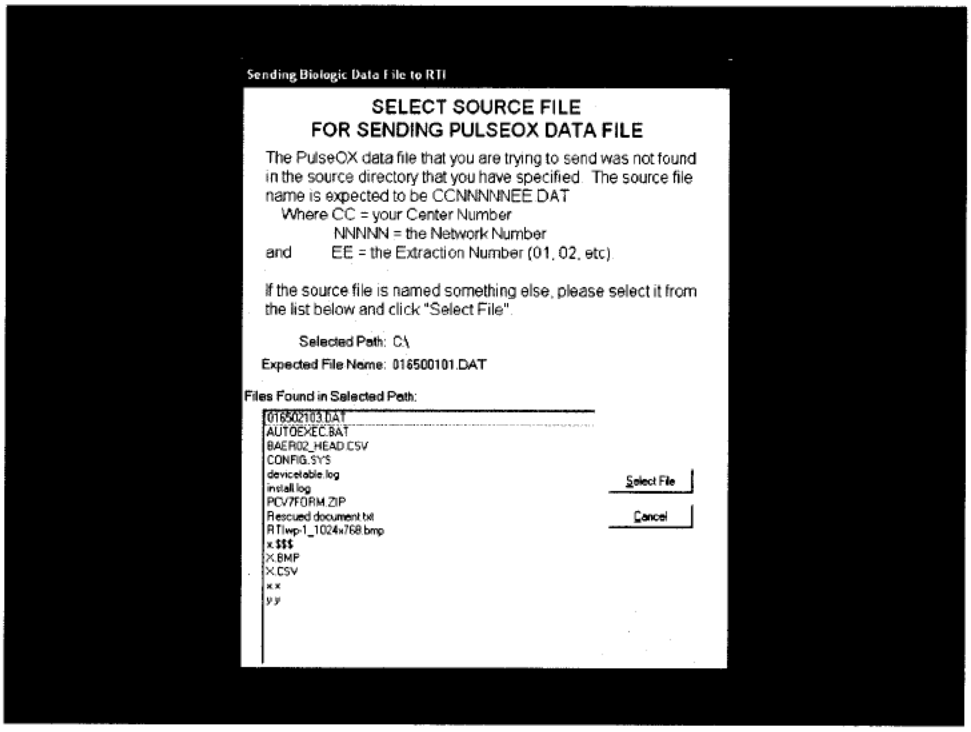


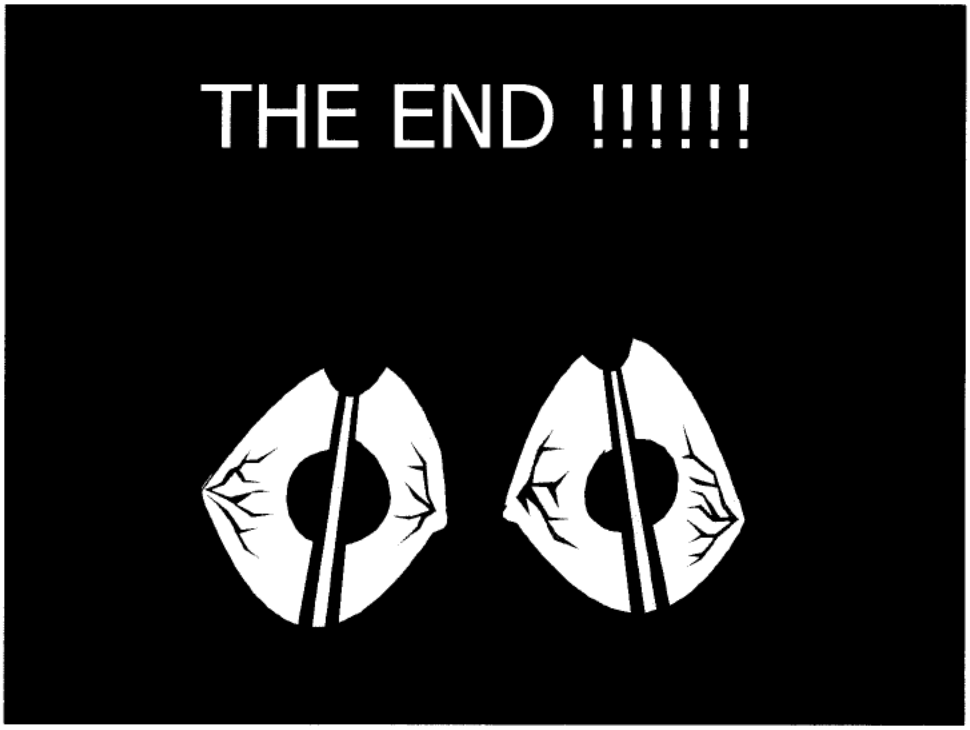












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

xxxx

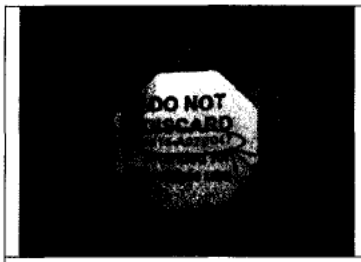
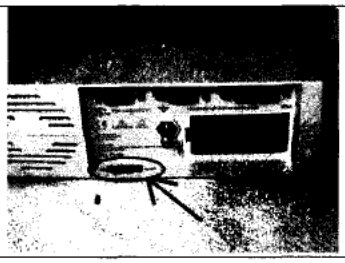
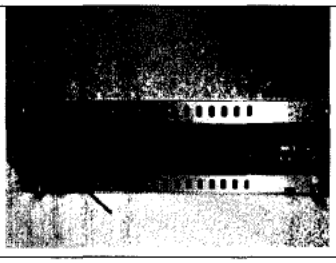
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006

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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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,

Michele Walsh, MD

Abbot Laptook, MD

Kurt Schibler, MD

Bradley Yoder, MD

Roger Faix, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Marie Gantz, PhD

Nancy Newman, 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
Tufts NEMC (23)	Ivan Frantz, MD	Ivan Frantz, MD
University of Iowa (24)	Edward Bell, MD	Edward Bell, MD
University of Utah (25)	Roger Faix, MD	Bradley, Yoder, MD
University of New Mexico (26)	Kristi Watterberg, MD	Kristi Watterberg, 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. Any subsequent extubations will also follow standard practice.

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. $pC0_2$:

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
SUPP05 and SUPP05A

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

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 results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**

Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. 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.

For all other time points enter the FiO_2 and Mode of Support.

c. pH

Record the acid base status of the blood.

d. $C0_2$

e. PO_2:

f. FiO_2

Record the **FiO_2** at the time the blood gas was collected or at other scheduled time points.

g. Source:

Record the source of the blood gas

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

i. If Mode =5 record Flow Rate

Record the flow rate for infants on nasal cannula

4. If Mode of Support =4 (CPAP), type used:

Record the type of CPAP

2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

13. Oximeter Alarm Check.

The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine.

The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

14. 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

15. Was the infant intubated or extubated on this day?
If Yes, Complete Section B and/or Section C of the SUPP05A

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

Section B

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 information prior to intubation:
Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record ""*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code ""*
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
4. Saturation

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 Kris Zaterka-Baxter 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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= No Support all day and off the study oximeter*.

  * Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b) [redacted]

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.


Select the → button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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.

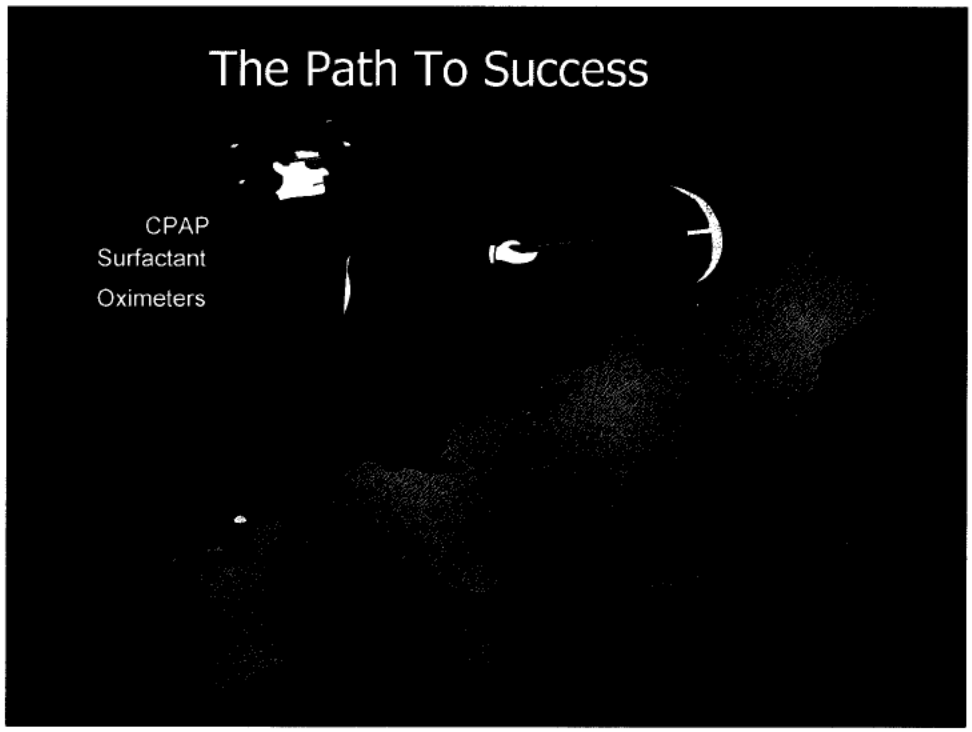
Parent's or legal guardian's signature	DATE
Relationship of legal guardian to subject	DATE
Signature of person explaining and getting consent	DATE

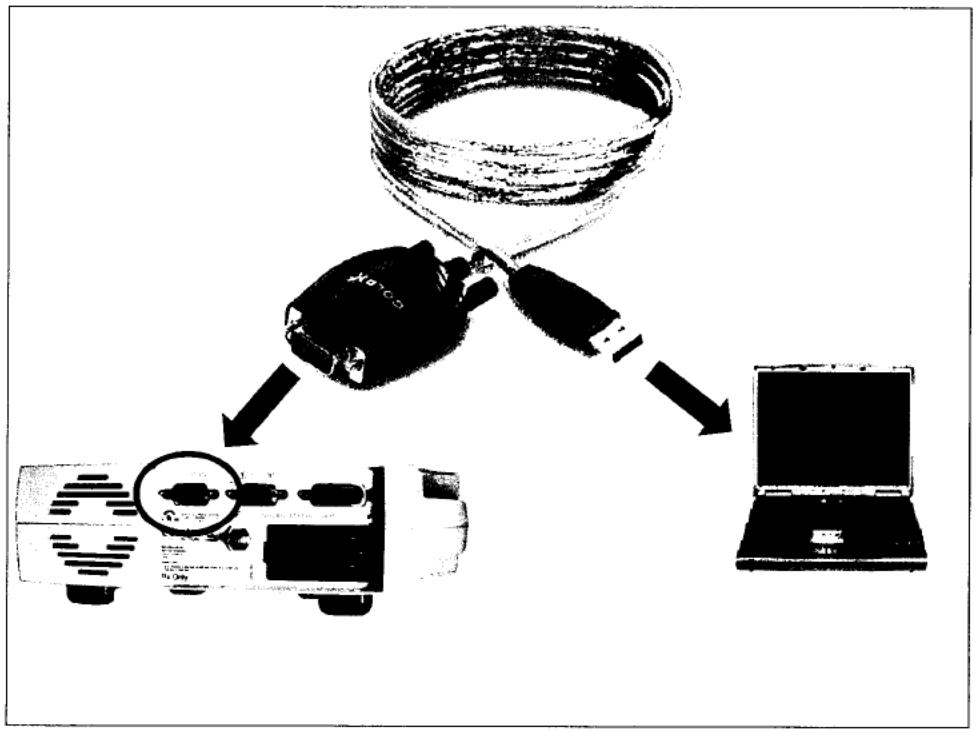
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

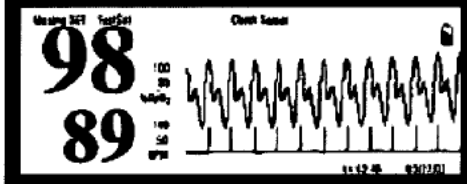
Use arrow key to select "Binary".

Select button.

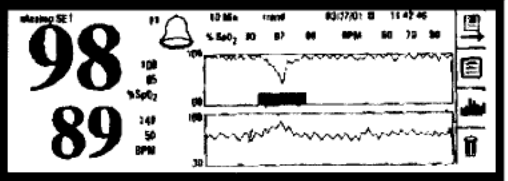
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

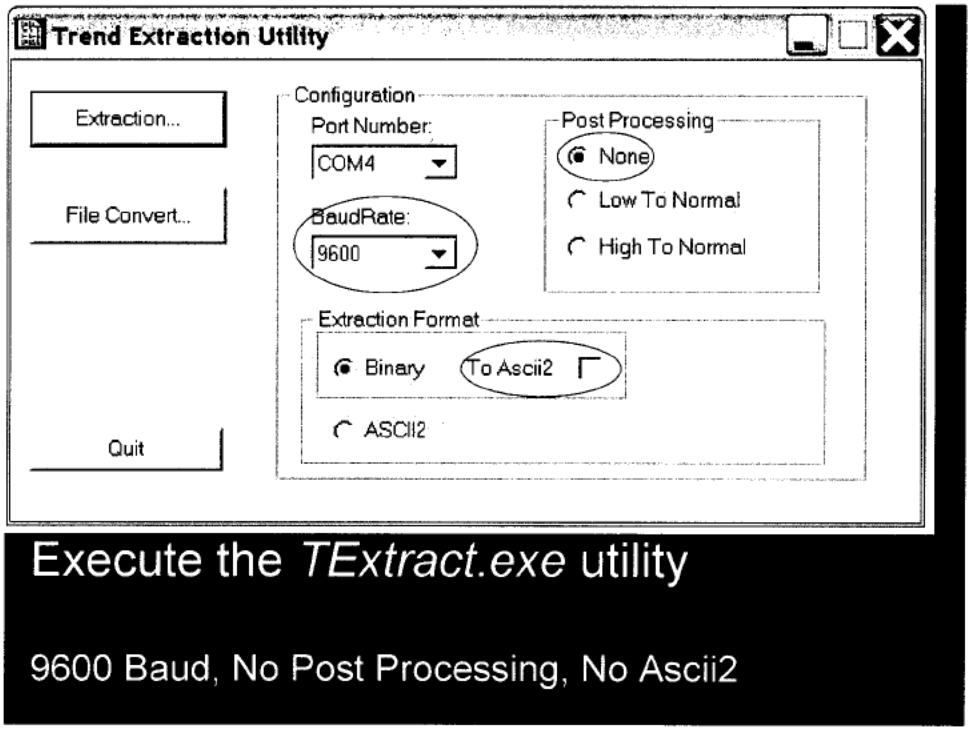
Make sure the Radical is in run mode and not in mode.



YES

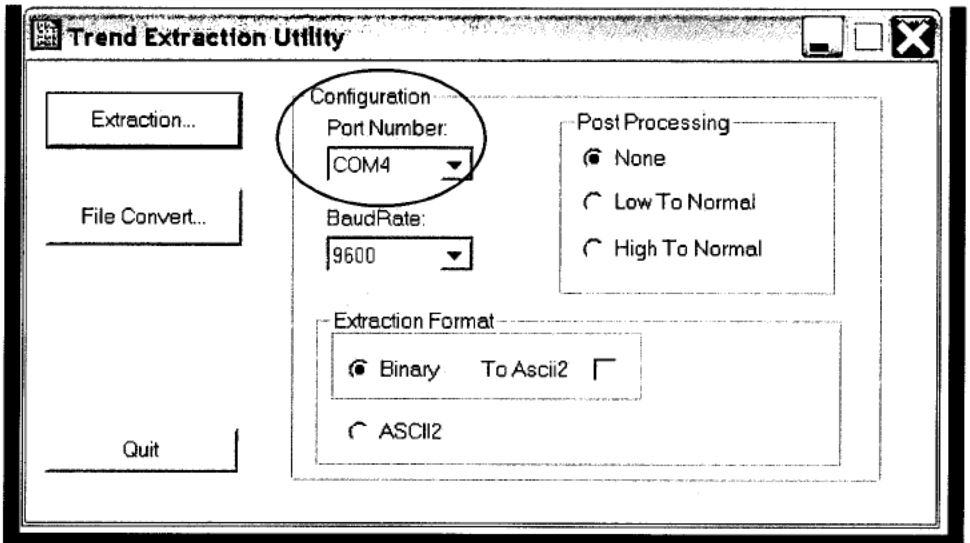


No

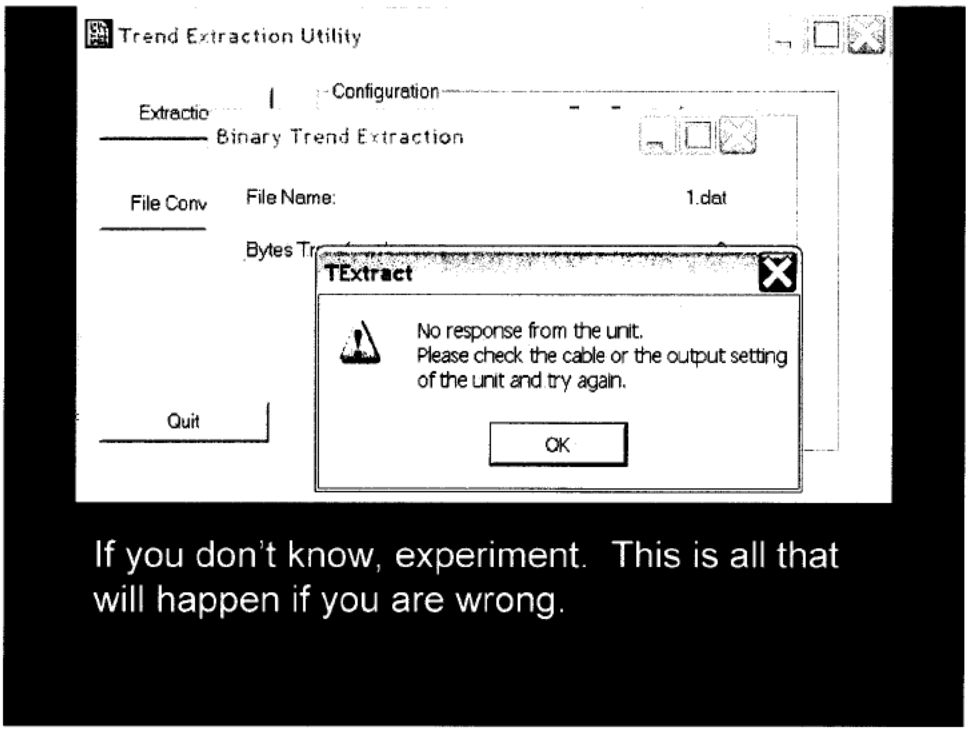


Execute the *TExtract.exe* utility

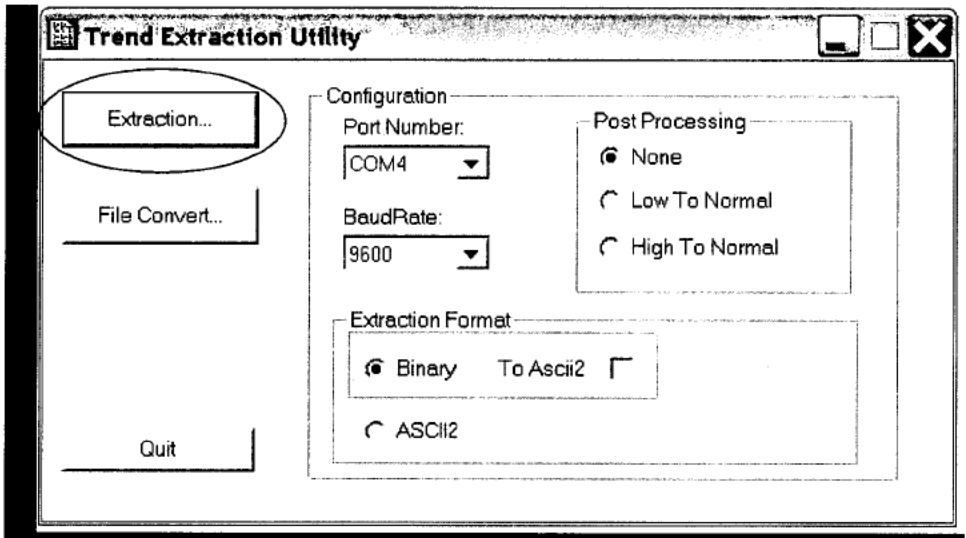
9600 Baud, No Post Processing, No Ascii2



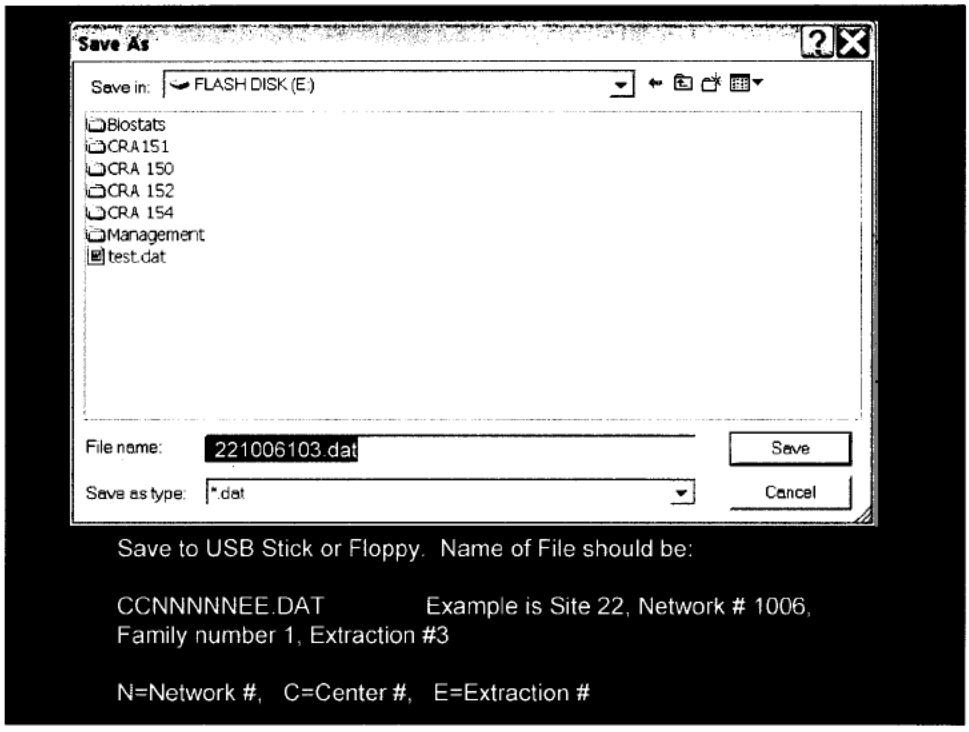
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.



If you don't know, experiment. This is all that will happen if you are wrong.



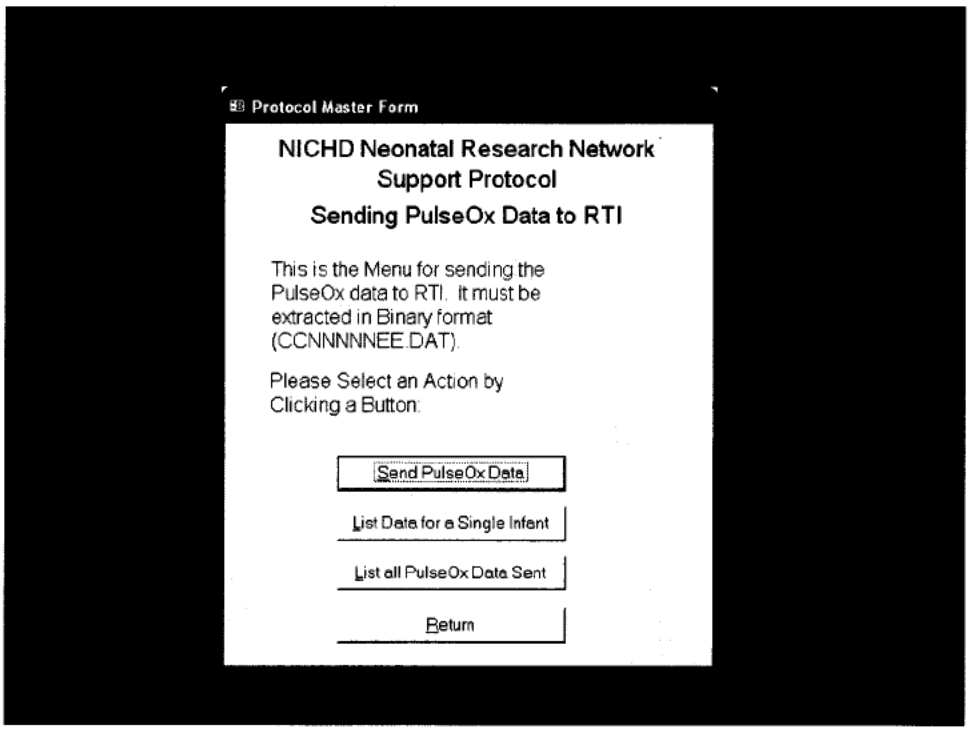
Hit Extraction.

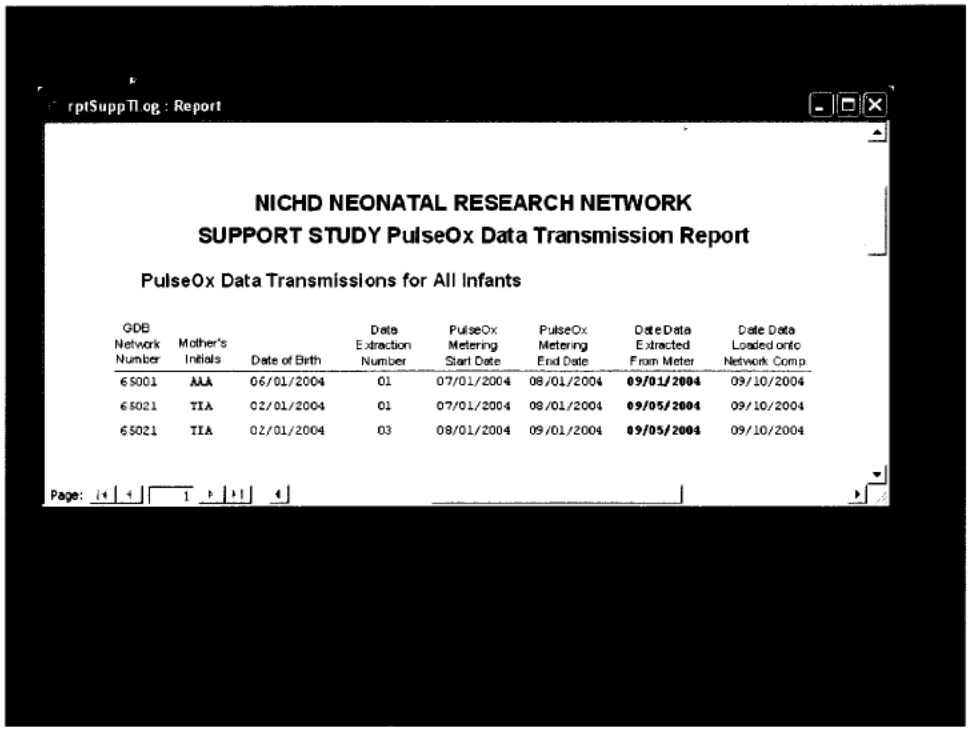


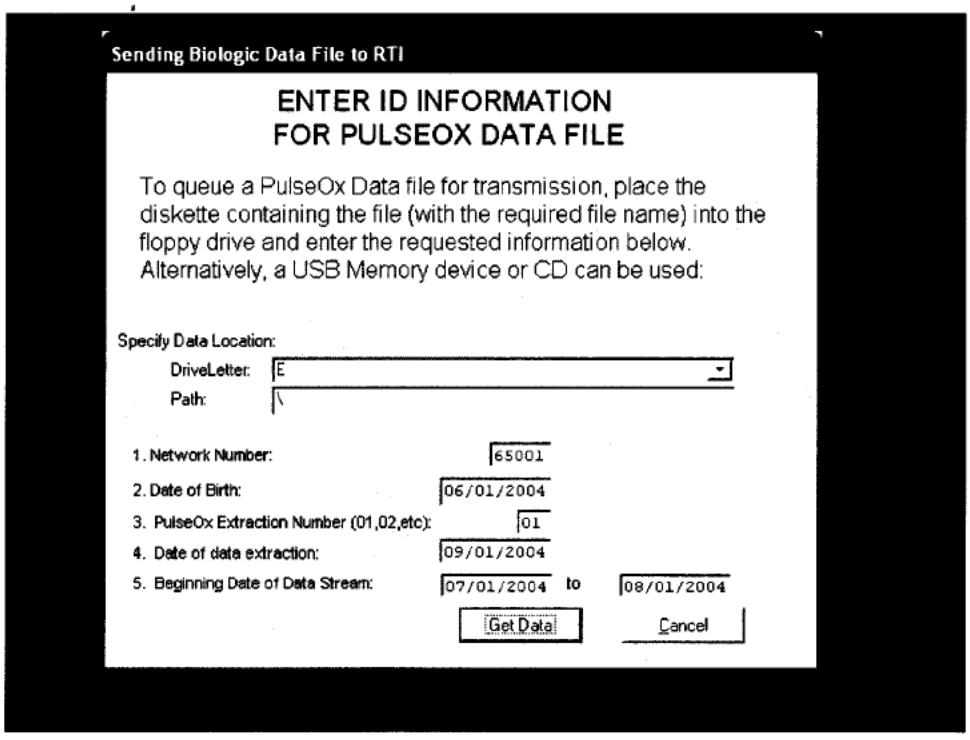
Save to USB Stick or Floppy. Name of File should be:

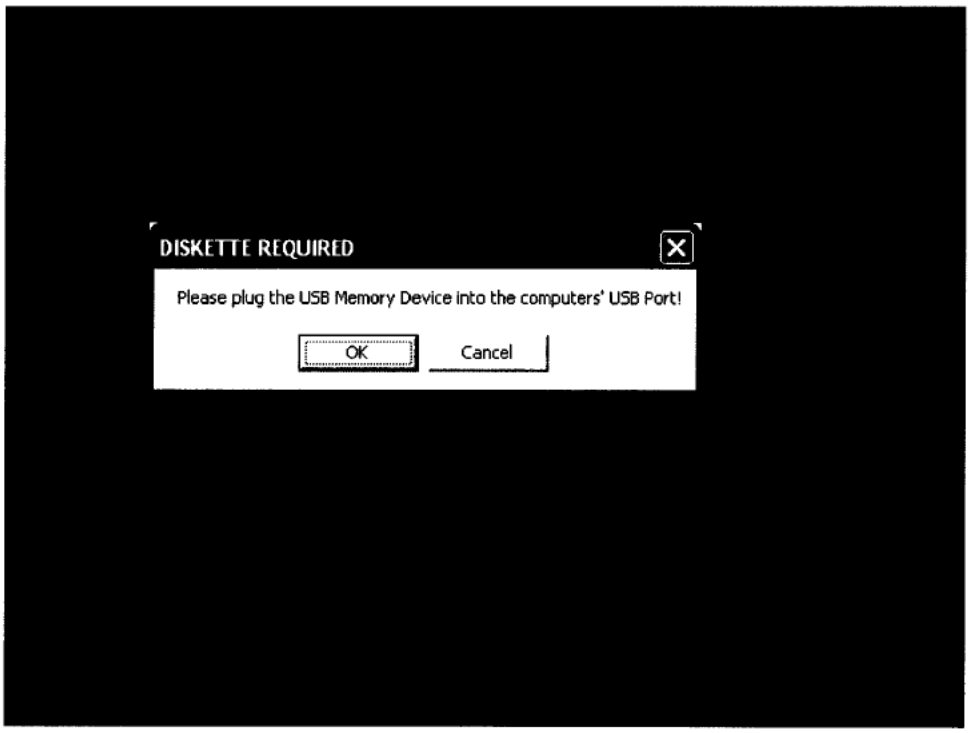
CCNNNNNEE.DAT Example is Site 22, Network # 1006, Family number 1, Extraction #3

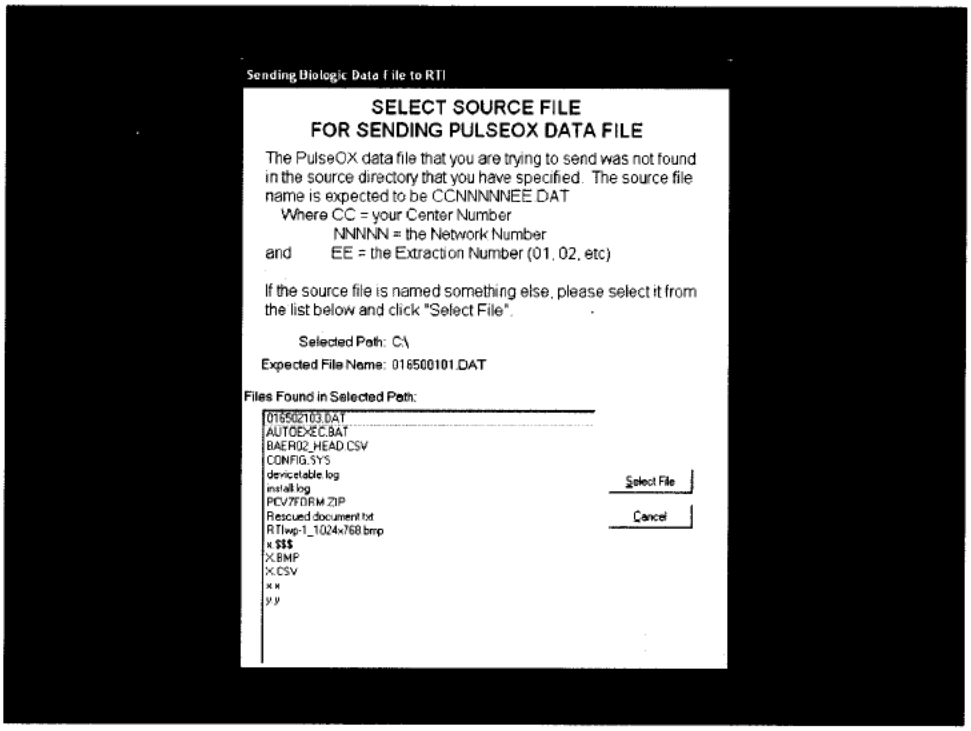
N=Network #, C=Center #, E=Extraction #

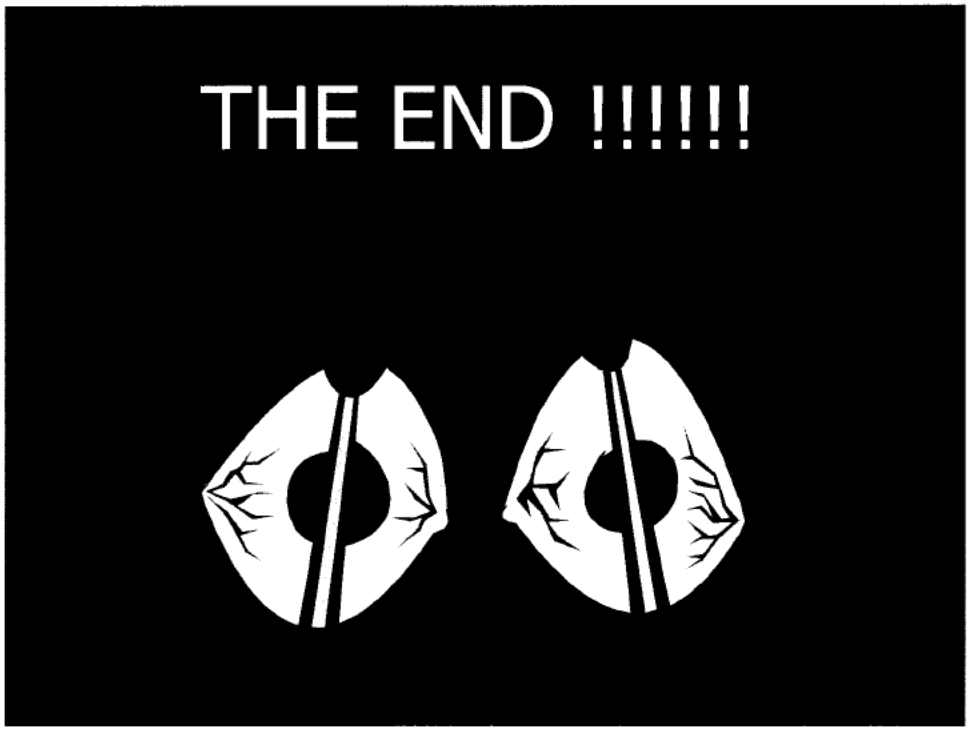












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED **M**ATERIAL **A**UTHORIZATION

 # xxxx

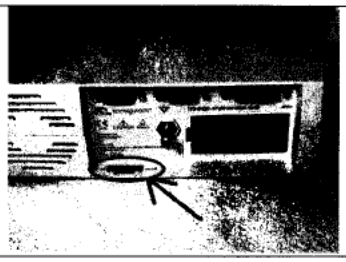
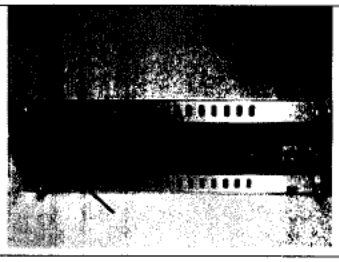
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

This form should be completed if more than one intubation/extubation occurs in the same day.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/____

Study Day	15 __/__/____ Month Day Year	16 __/__/____ Month Day Year	17 __/__/____ Month Day Year	18 __/__/____ Month Day Year	19 __/__/____ Month Day Year	20 __/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	21 __ __/__ __/__ __ __ __ Month Day Year	22 __ __/__ __/__ __ __ __ Month Day Year	23 __ __/__ __/__ __ __ __ Month Day Year	24 __ __/__ __/__ __ __ __ Month Day Year	25 __ __/__ __/__ __ __ __ Month Day Year	26 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: ___

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___ / ___ / _____

Study Day	27	28	29	30	31	32
	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	33 __ __/__ __/__ __ __ __ Month Day Year	34 __ __/__ __/__ __ __ __ Month Day Year	35 __ __/__ __/__ __ __ __ Month Day Year	36 __ __/__ __/__ __ __ __ Month Day Year	37 __ __/__ __/__ __ __ __ Month Day Year	38 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___ ___ / ___ ___ / ___ ___ ___ ___

Study Day	39 ___ ___/___ ___/___ ___ ___ ___ Month Day Year	40 ___ ___/___ ___/___ ___ ___ ___ Month Day Year	41 ___ ___/___ ___/___ ___ ___ ___ Month Day Year	42 ___ ___/___ ___/___ ___ ___ ___ Month Day Year	43 ___ ___/___ ___/___ ___ ___ ___ Month Day Year	44 ___ ___/___ ___/___ ___ ___ ___ Month Day Year
1. Scheduled Time: 06:00	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.
(d) Oximeter Alarm Check	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___
2. Scheduled Time: 12:00	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.
(d) Oximeter Alarm Check	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___
3. Scheduled Time: 18:00	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.
(d) Oximeter Alarm Check	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___
4. Scheduled Time: 23:59	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)	___ ___ : ___ ___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.	___ ___ . ___ ___ Liters/Min.
(d) Oximeter Alarm Check	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___	___ ___ : ___ ___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	45	46	47	48	49	50
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	51 __ __/__ __/__ __ __ __ Month Day Year	52 __ __/__ __/__ __ __ __ Month Day Year	53 __ __/__ __/__ __ __ __ Month Day Year	54 __ __/__ __/__ __ __ __ Month Day Year	55 __ __/__ __/__ __ __ __ Month Day Year	56 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: _ _ _ _ _ Birth No: ___ Mother's Initials: _ _ _

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	57	58	59	60	61	62
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	63 __ __/__ __/__ __ __ __ Month Day Year	64 __ __/__ __/__ __ __ __ Month Day Year	65 __ __/__ __/__ __ __ __ Month Day Year	66 __ __/__ __/__ __ __ __ Month Day Year	67 __ __/__ __/__ __ __ __ Month Day Year	68 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	69 __ __/__ __/__ __ __ __ Month Day Year	70 __ __/__ __/__ __ __ __ Month Day Year	71 __ __/__ __/__ __ __ __ Month Day Year	72 __ __/__ __/__ __ __ __ Month Day Year	73 __ __/__ __/__ __ __ __ Month Day Year	74 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	75 __ __/__ __/__ __ __ __ Month Day Year	76 __ __/__ __/__ __ __ __ Month Day Year	77 __ __/__ __/__ __ __ __ Month Day Year	78 __ __/__ __/__ __ __ __ Month Day Year	79 __ __/__ __/__ __ __ __ Month Day Year	80 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	81 ___/___/_____ Month Day Year	82 ___/___/_____ Month Day Year	83 ___/___/_____ Month Day Year	84 ___/___/_____ Month Day Year	85 ___/___/_____ Month Day Year	86 ___/___/_____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

From: Petrie, Carolyn
To: Petrie, Carolyn; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Michele Walsh; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; nxs5@cwru.edu; wrich@ucsd.edu; Gantz, Marie
Cc: Zaterka-Baxter, Kristin; cdg2749@yahoo.com; msumner@peds.uab.edu; fmartinez@ucsd.edu; bvecchio@careNE.org
Subject: SUPPORT conference call, Mon Jun 19, 12-1pm ET
Date: Monday, June 05, 2006 3:24:10 PM

The best available time for the SUPPORT group to meet via teleconference is

Monday, June 19
12:00-1:00pm ET

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

We are not using the fancy presentation system, so this will be a regular conference call with the SUPPORT Subcommittee.

From:	Zaterka-Baxter, Kristin
To:	wcarlo@peds.uab.edu; mcw3@cwru.edu; bradley.yoder@hsc.utah.edu; Roger.faix@hsc.utah.edu; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Nancy Newman; Wade Rich; Gantz, Marie
Cc:	Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Petrie, Carolyn; Neil Finer
Subject:	FW: SUPP05A
Date:	Friday, June 02, 2006 12:04:51 PM
Attachments:	SUP09.doc SUPPORT Manual[Updated06.05.06 uc].doc SUPP05ASafetyMonitor[06.05.06 v2.1(uc)]Rev.doc SUPP11[Rev 06.05.06 uc] .doc

Hello everyone,

There have been a few revisions made to the Support manual and two study forms. These revisions were primarily based on discussion during the last coordinators conference call. Please note that changes made to Chapter 10 and form SUPP05a were prompted by RTI so that we can program the data entry system to allow cleaner data to be obtained for analysis. Please find attached a drafted technical memo outlining these revisions and the revised manual and forms with all changes highlighted for your review. Please send any comments and/or suggestions by Friday June 9th.

Thanks,
Kris

Kris Zaterka-Baxter, RN, CCRP
RTI International
4426 South Miami Blvd.
Durham, NC 27703
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kzaterka@rti.org

RTI INTERNATIONAL | **Memorandum**

June 5, 2006

SUPPORT TECHNICAL MEMO # 9

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Clarifications to the Manual of Procedures/Forms

The following items have been clarified in the Manual of Procedures:

Chapter 5
Clarification was requested during the April 2006 coordinators conference call regarding manual guidelines for extubation after re-intubation for the control (surfactant) arm. The following underlined text has been added to page 5-4, section 5.1.8 (3) Reintubation:

Control Infants may be reintubated using Standard of Care. Any subsequent extubation will also follow standard practice.

Chapter 10 (Section 10.2.2, page 10-3)
When programming the revision to form SUPP05a per the March 7, 2006 technical memo, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report. Therefore, we have deleted Section C as suggested in March and modified this forms to allow each event to be reported separately.

Please note that this version supersedes the revision in March which was not programmed. This version requests the same data as the previous version dated 10/03/2005 with the addition of a date and time for each event:

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

ADDED: **Report Number**

Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day

Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date

Record the date in which the intubation/extubation occurred.

Section B

Section 10.2.3 (Section C) has been deleted. Highlighted chapter is enclosed.

Form SUPP05a *has been revised to reflect this revision (version 2.1; dated 06/05/06). Highlighted form enclosed*

Chapter 16
A request was made during the May 2006 coordinators conference call to add a code identifying infants who are in no support all day and off the study oximeter for any days between day 15 through 36 weeks. The following underlined text has been added to page 16-1, section 16.1.1 (bullet 3):

Highest Level of Support
Record the highest level of support the infant is in at the scheduled time points during this STUDY day.
Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
7= No Support, 9= No Support all day and off the study oximeter*.

* Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

Form Supp11 *has been modified to include Code 9 (version 2.1; dated 06/05/06).*

The updated Manual of Procedures and forms SUPP05a and SUPP11 have been posted on the Neonatal Web site with the revision date of 06/05/06.

cc: Rosemary Higgins

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006

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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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. **Any subsequent extubations will also follow standard practice.**

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 $Sa0_2$ ≥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
SUPP05 and SUPP05A

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

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 results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**

Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. 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.

For all other time points enter the FiO_2 and Mode of Support.

c. pH

Record the acid base status of the blood.

d. $C0_2$

e. PO_2:

f. FiO_2

Record the **FiO_2** at the time the blood gas was collected or at other scheduled time points.

g. Source:

Record the source of the blood gas

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

i. If Mode =5 record Flow Rate

Record the flow rate for infants on nasal cannula

4. If Mode of Support =4 (CPAP), type used:

Record the type of CPAP

2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

13. Oximeter Alarm Check.

The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine.

The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

14. 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

15. Was the infant intubated or extubated on this day?
If Yes, Complete Section B and/or Section C of the SUPP05A

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes"**. If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

Section B

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 information prior to intubation:
Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record ""*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code ""*
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. **Desaturation?** Record Yes if the infant experienced desaturations requiring intubation on this day
~~9.~~ **10. 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
4. Saturation

~~**10.2.3 Section C. Intubation/Extubation Information (For NICU ONLY)**~~
~~**If more than one intubation/extubation occurs in one day, complete Section C.**~~
~~Record the intubation/extubation history for each Study Day 1- 14.~~
~~**1. Did the infant have more than one intubation/extubation on this day?**~~
~~**If Yes,**~~
~~**2. 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 information prior to intubation:~~
~~*Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record "*"*~~
~~*Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code "*"*~~
~~**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 thisday.~~

~~**9. Other (specify).** Record Yes if the infant had other conditions this day. **Specify these.**~~

~~**3. 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**~~

~~**4. Saturation**~~

~~***NOTE: If more than two intubations/extubations were performed, complete additional SUPP05A, Section C for this study day.***~~

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 Kris Zaterka-Baxter 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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, **9= No Support all day and off the study oximeter***.

  *** Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.**

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337(b) (6)

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

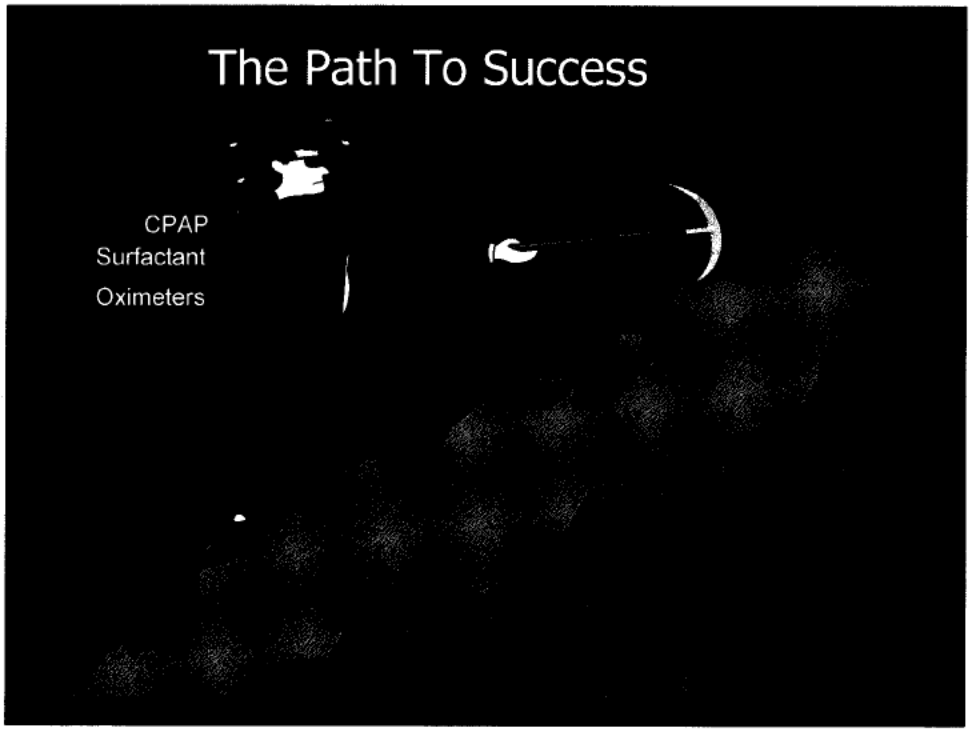
Signature of person explaining and getting consent DATE

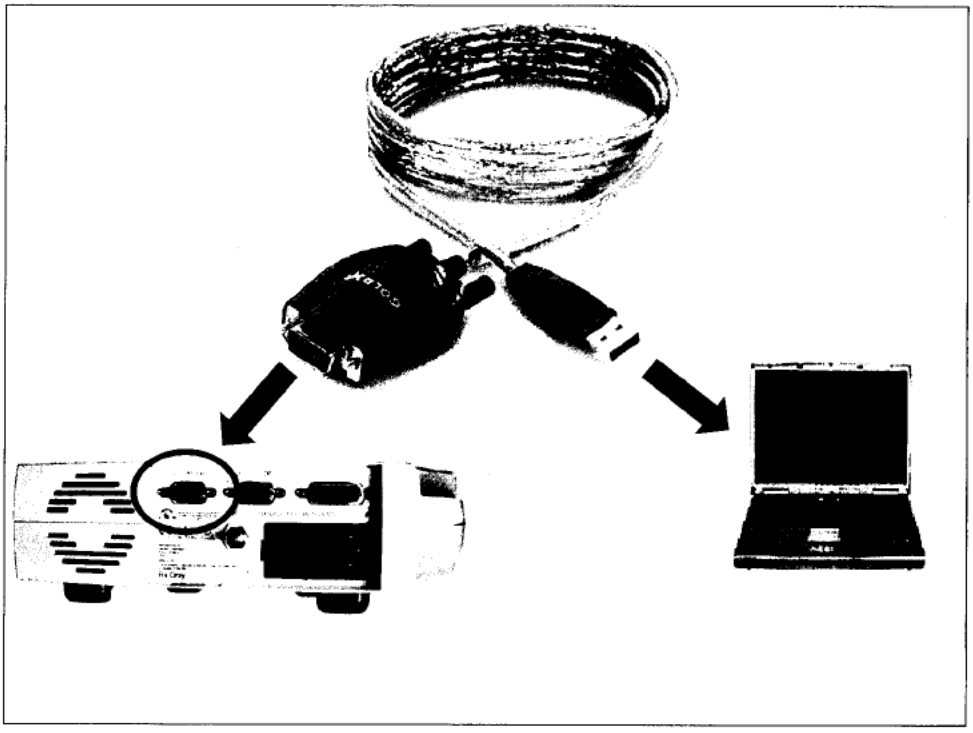
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

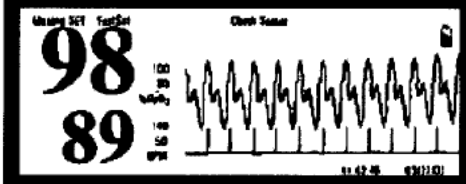
Use arrow key to select "Binary".

Select button.

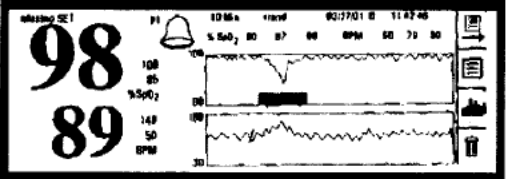
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

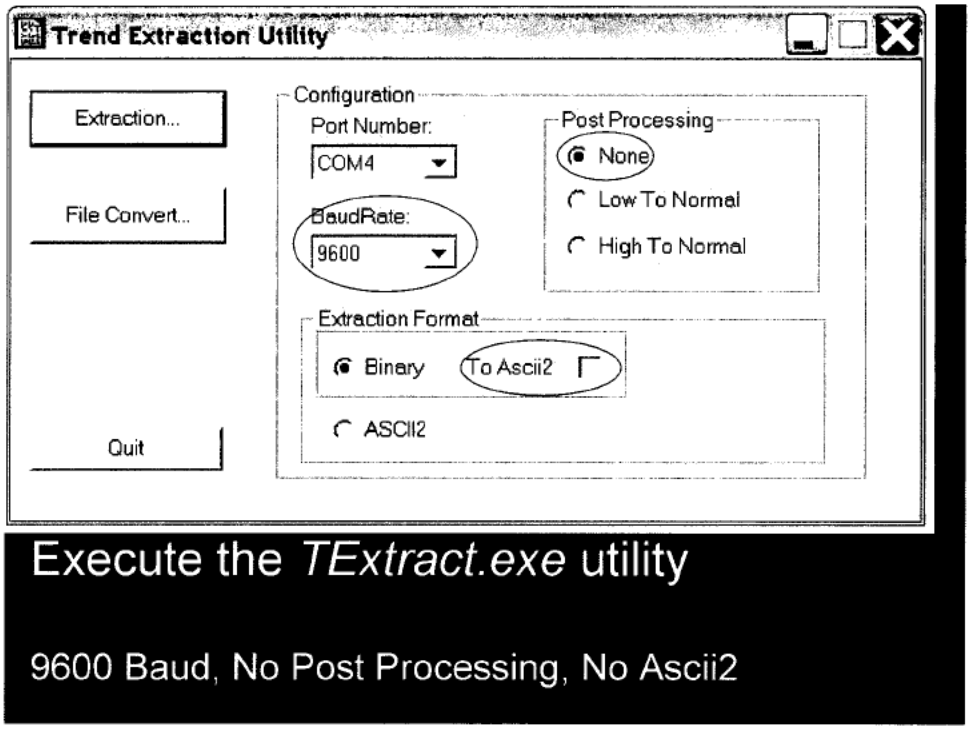
Make sure the Radical is in run mode and not in mode.



YES

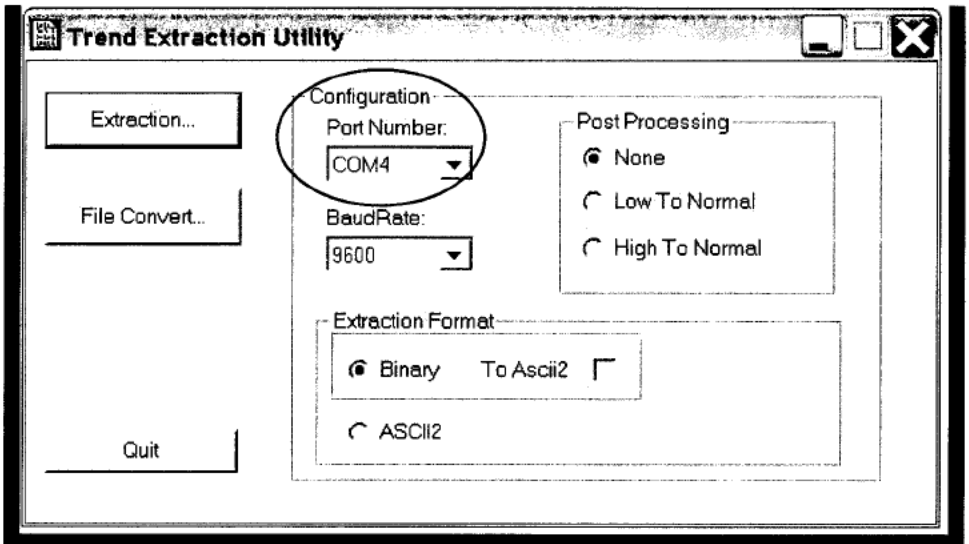


No

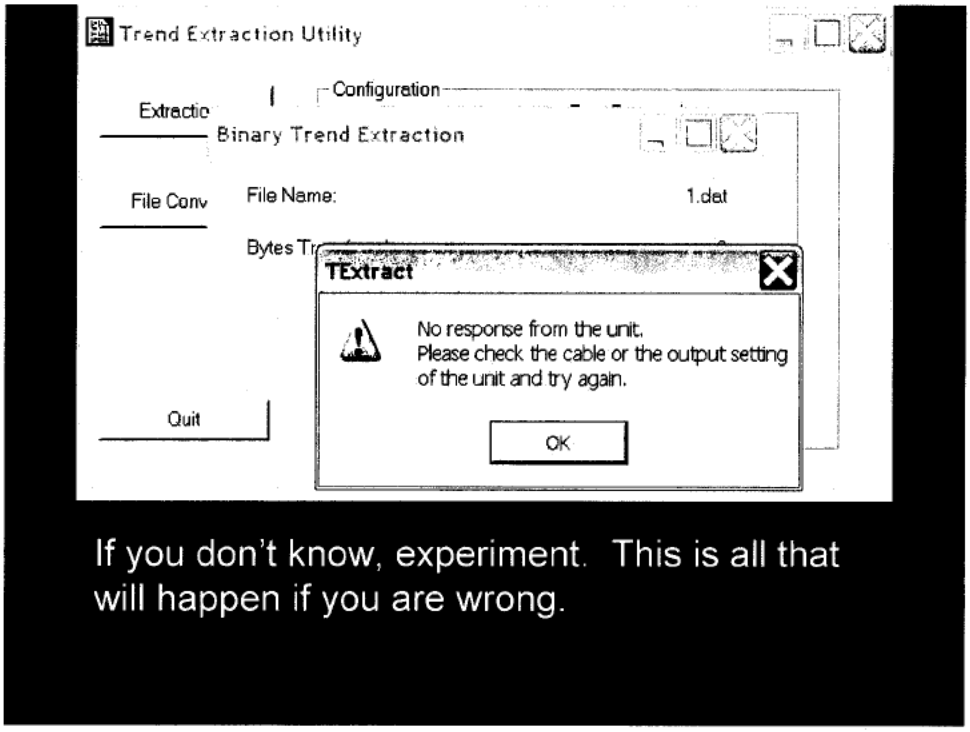


Execute the *TExtract.exe* utility

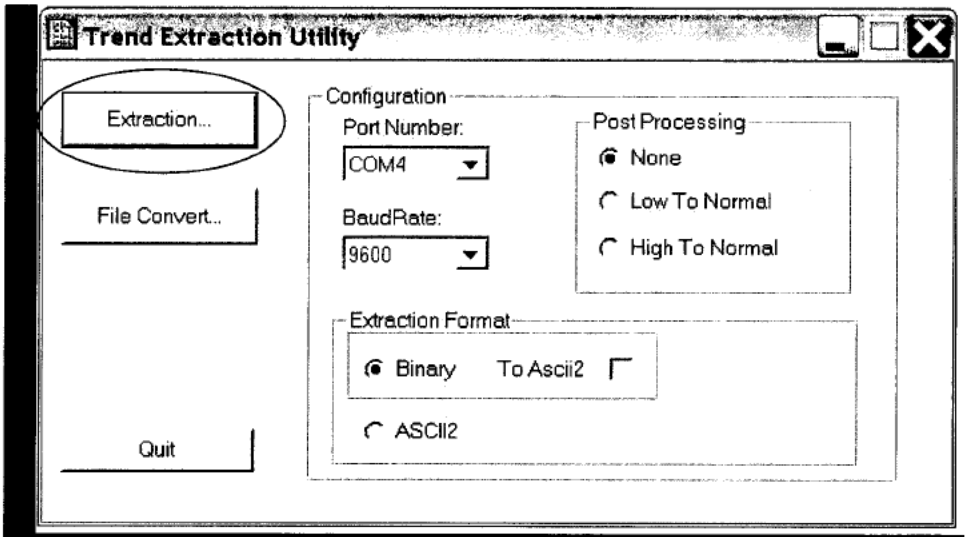
9600 Baud, No Post Processing, No Ascii2



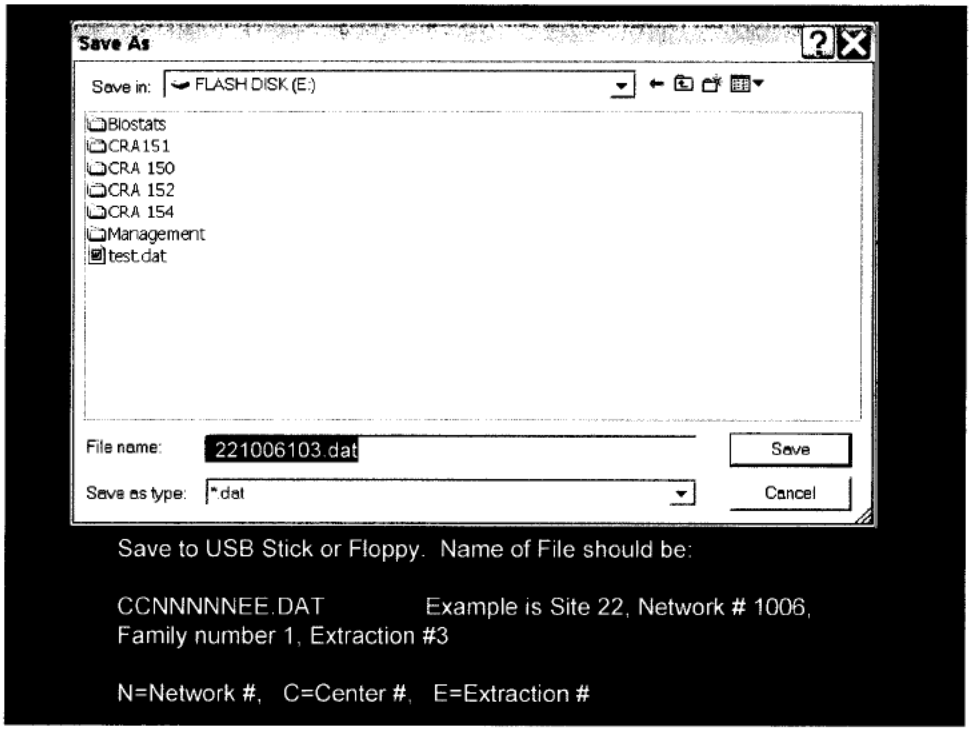
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.



If you don't know, experiment. This is all that will happen if you are wrong.



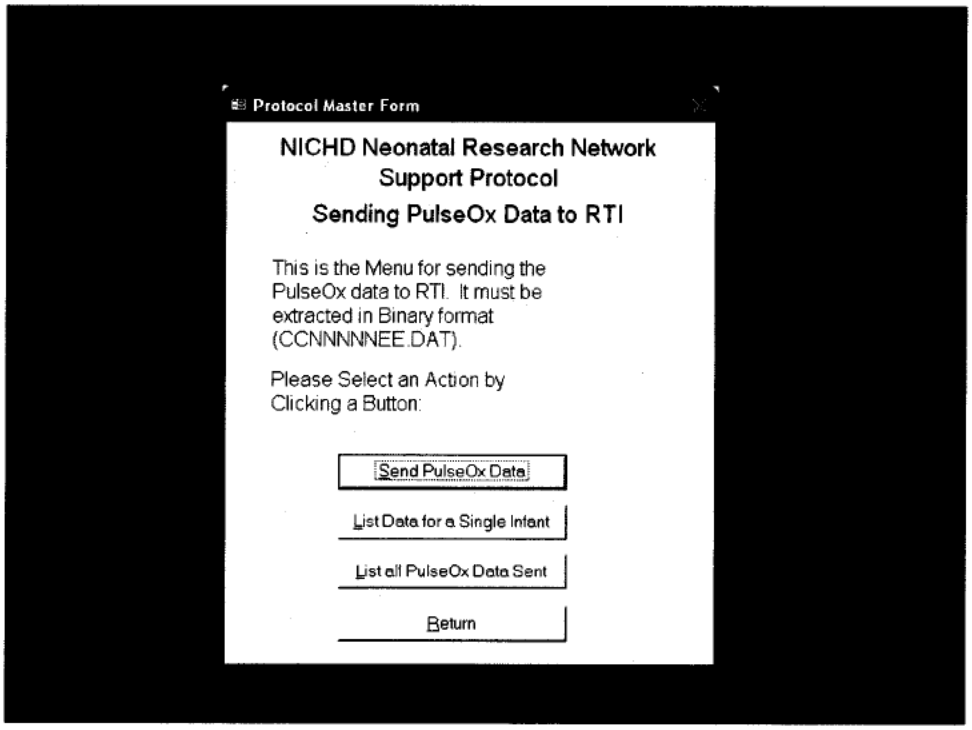
Hit Extraction.

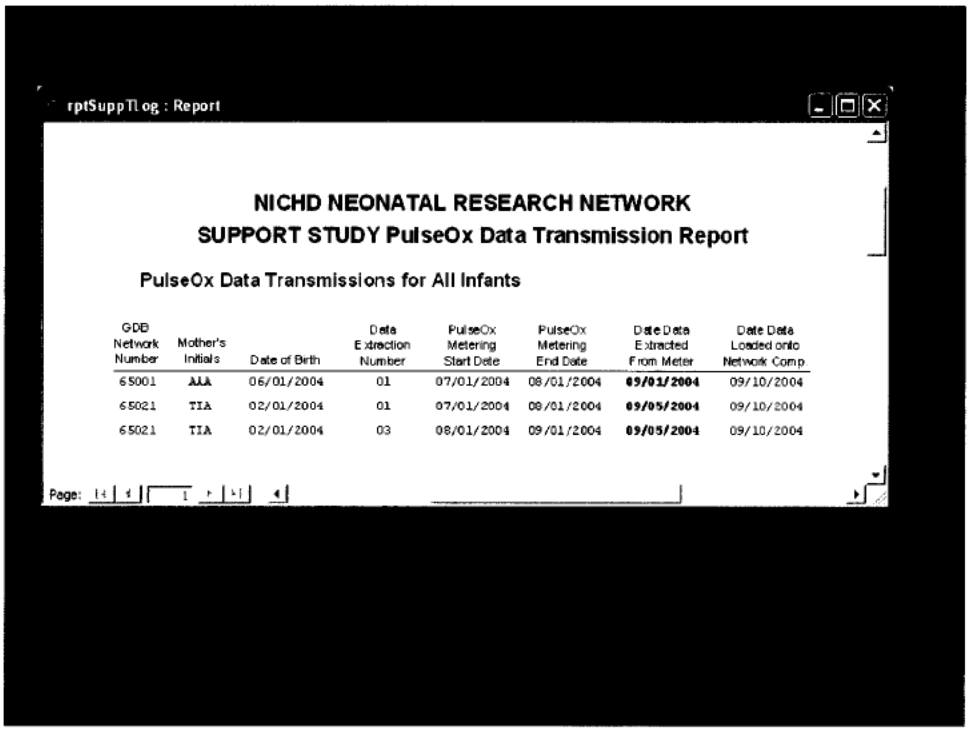


Save to USB Stick or Floppy. Name of File should be:

CCNNNNNEE.DAT Example is Site 22, Network # 1006, Family number 1, Extraction #3

N=Network #, C=Center #, E=Extraction #



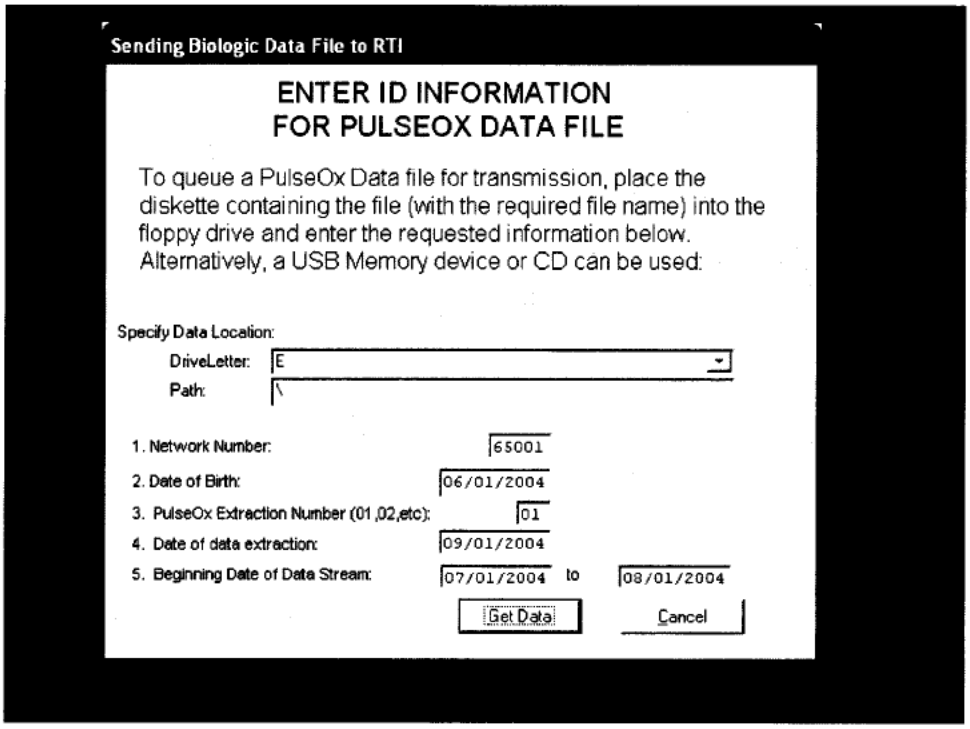

rptSuppTLog : Report

NICHD NEONATAL RESEARCH NETWORK
SUPPORT STUDY PulseOx Data Transmission Report

PulseOx Data Transmissions for All Infants

GDB Network Number	Mother's Initials	Date of Birth	Data Extraction Number	PulseOx Metering Start Date	PulseOx Metering End Date	Date Data Extracted From Meter	Date Data Loaded onto Network Comp
65001	AAA	06/01/2004	01	07/01/2004	08/01/2004	**09/01/2004**	09/10/2004
65021	TIA	02/01/2004	01	07/01/2004	08/01/2004	**09/05/2004**	09/10/2004
65021	TIA	02/01/2004	03	08/01/2004	09/01/2004	**09/05/2004**	09/10/2004

Page: 1


Sending Biologic Data File to RTI

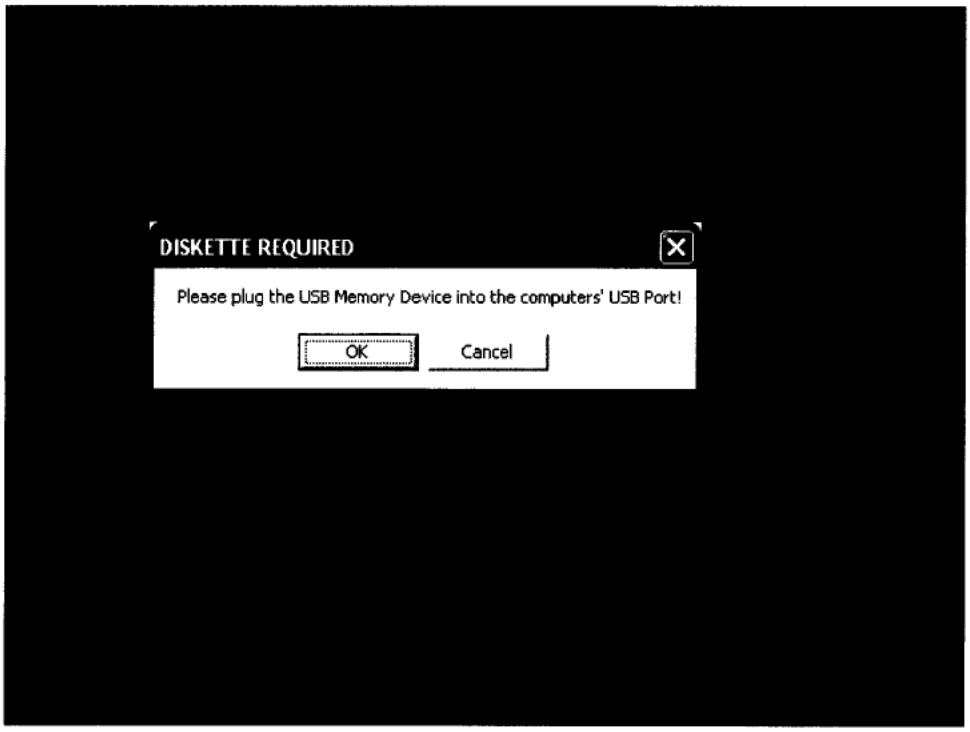
ENTER ID INFORMATION FOR PULSEOX DATA FILE

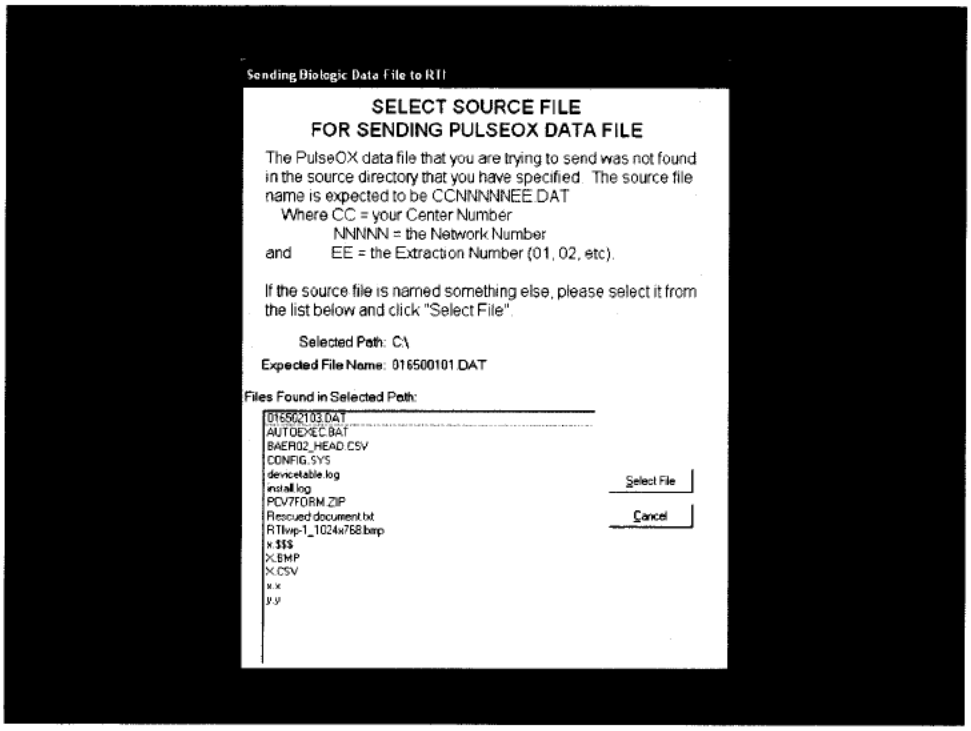
To queue a PulseOx Data file for transmission, place the diskette containing the file (with the required file name) into the floppy drive and enter the requested information below. Alternatively, a USB Memory device or CD can be used:

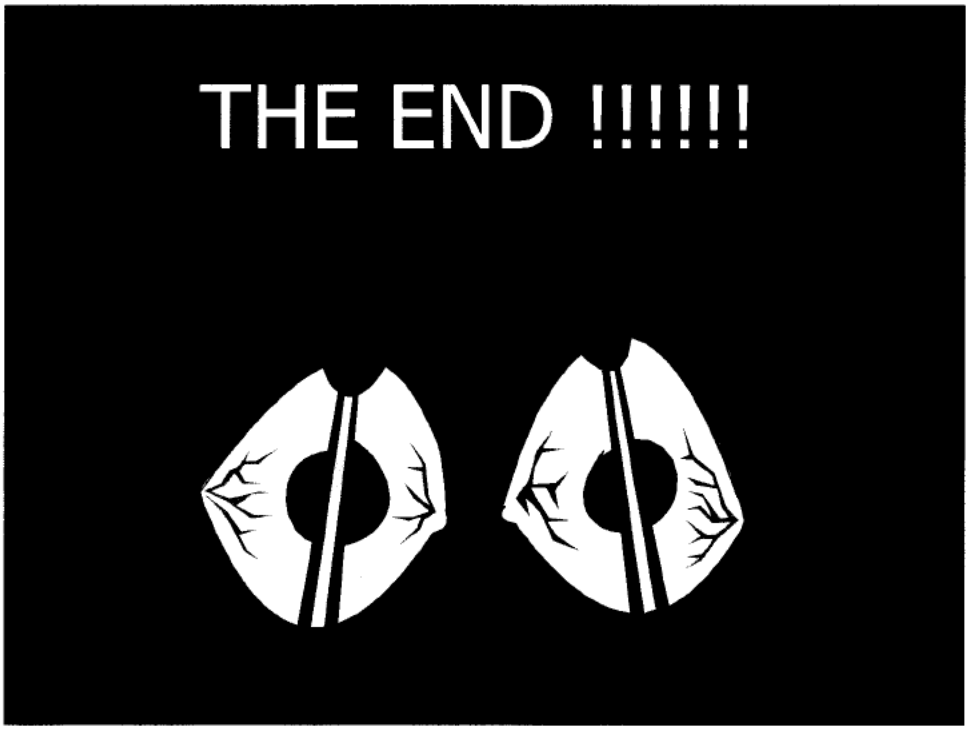
Specify Data Location:
DriveLetter: E
Path: \

1. Network Number: 65001
2. Date of Birth: 06/01/2004
3. PulseOx Extraction Number (01 ,02,etc): 01
4. Date of data extraction: 09/01/2004
5. Beginning Date of Data Stream: 07/01/2004 to 08/01/2004

Get Data Cancel







APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED MATERIAL AUTHORIZATION

 # xxxx

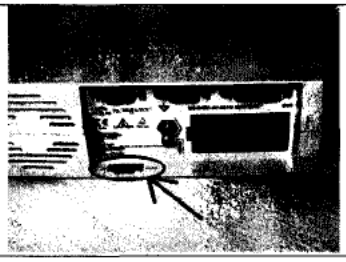
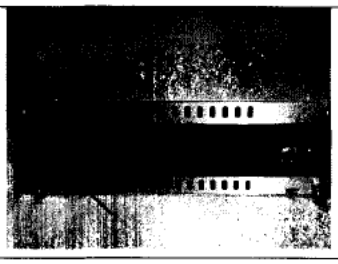
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
     (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
   Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

NICU Network

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPPORT Rel 3.0
Revised June 5, 2006

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

This form should be completed if more than one intubation/extubation occurs in the same day.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __** C.

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ____ / ____ / _____

Study Day	15 __ __/__ __/__ __ __ __ Month Day Year	16 __ __/__ __/__ __ __ __ Month Day Year	17 __ __/__ __/__ __ __ __ Month Day Year	18 __ __/__ __/__ __ __ __ Month Day Year	19 __ __/__ __/__ __ __ __ Month Day Year	20 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	21 __ __/__ __/__ __ __ __ Month Day Year	22 __ __/__ __/__ __ __ __ Month Day Year	23 __ __/__ __/__ __ __ __ Month Day Year	24 __ __/__ __/__ __ __ __ Month Day Year	25 __ __/__ __/__ __ __ __ Month Day Year	26 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/_____

Study Day	27 Month Day Year	28 Month Day Year	29 Month Day Year	30 Month Day Year	31 Month Day Year	32 Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ____ / ____ / ____

Study Day	33 __ __/__ __/__ __ __ __ Month Day Year	34 __ __/__ __/__ __ __ __ Month Day Year	35 __ __/__ __/__ __ __ __ Month Day Year	36 __ __/__ __/__ __ __ __ Month Day Year	37 __ __/__ __/__ __ __ __ Month Day Year	38 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	39	40	41	42	43	44
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ __ / __ __ __ / __ __ __ __

Study Day	45	46	47	48	49	50
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO	YES | NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	51 __ __/__ __/__ __ __ __ Month Day Year	52 __ __/__ __/__ __ __ __ Month Day Year	53 __ __/__ __/__ __ __ __ Month Day Year	54 __ __/__ __/__ __ __ __ Month Day Year	55 __ __/__ __/__ __ __ __ Month Day Year	56 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	57 __ __/__ __/__ __ __ __ Month Day Year	58 __ __/__ __/__ __ __ __ Month Day Year	59 __ __/__ __/__ __ __ __ Month Day Year	60 __ __/__ __/__ __ __ __ Month Day Year	61 __ __/__ __/__ __ __ __ Month Day Year	62 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	63 __ __/__ __/__ __ __ __ Month Day Year	64 __ __/__ __/__ __ __ __ Month Day Year	65 __ __/__ __/__ __ __ __ Month Day Year	66 __ __/__ __/__ __ __ __ Month Day Year	67 __ __/__ __/__ __ __ __ Month Day Year	68 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

RESPIRATORY SUPPORT AFTER 14 DAYS

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: _ _ _ _ _ _ Birth No: ___ Mother's Initials: _ _ _

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __/__ __/__ __ __ __

Study Day	69 __ __/__ __/__ __ __ __ Month Day Year	70 __ __/__ __/__ __ __ __ Month Day Year	71 __ __/__ __/__ __ __ __ Month Day Year	72 __ __/__ __/__ __ __ __ Month Day Year	73 __ __/__ __/__ __ __ __ Month Day Year	74 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	75	76	77	78	79	80
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

RESPIRATORY SUPPORT AFTER 14 DAYS

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	81 ___/___/_____ Month Day Year	82 ___/___/_____ Month Day Year	83 ___/___/_____ Month Day Year	84 ___/___/_____ Month Day Year	85 ___/___/_____ Month Day Year	86 ___/___/_____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPP05A
Date: Friday, June 02, 2006 9:32:57 AM

Hi,
Dr. Finer has agreed to the changes made in Support. Does the Support subcommittee now need to review the revised manual and two forms prior to distribution? Have you had a chance to review the changes? I've drafted an email to the subcommittee if I need to send it out.

Thanks,
Kris

RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 01, 2006 3:05 PM
To: Zaterka-Baxter, Kristin
Cc: Wade Rich
Subject: RE: SUPP05A

Thanks Kris
These look fine to me
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, June 01, 2006 11:18 AM
To: Neil Finer; Nancy Newman; Wade Rich; Nancy Newman
Cc: Schaefer, Scott E.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Petrie, Carolyn; Gantz, Marie
Subject: RE: SUPP05A

Hi,
Please find attached a drafted technical memo outlining the following revisions to the manual and forms based on discussion during the last coordinators conference call. Please note that the added code on the SUPP11 form has been numbered '9' because code '8' existed in a prior version of this form that was subsequently removed so we can not use code 8 again for different data.

Please also note the revision to Chapter 10 and form SUPP05a was prompted by RTI to program the data entry system to allow cleaner data to be obtained for analysis and supersedes revisions made to this form on 03/07/06 (technical memo #6).

Also attached are the highlighted manual and corresponding forms. Please note that per Dr. Finer's email, we have deleted the question on desaturations in form SUPP05a and this event will continue to be recorded under 'other (specify)'.

Please take a moment and review these documents. We would like to send them out to the rest of the subcommittee to view prior to distribution and activation by the whole group.

Thanks,

Kris

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4426 South Miami Blvd.
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Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 01, 2006 1:04 PM
To: Nancy Newman; Wade Rich; Zaterka-Baxter, Kristin; Nancy Newman
Cc: Schaefer, Scott E.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP05A

Hello Nancy
I appreciate your concerns and your desire to provide specific documentation for events in the trial.
Within the SUPPORT protocol we have criteria for re-intubation for infants randomized to CPAP in the DR, and no such criteria for Control-Surfactant infants. Control-Surfactant infants who are initially extubated are reintubated following unit standard of care.
For CPAP infants we have stated intubation-reintubation criteria that are applicable for 14 days and provide specific conditions/criteria for intubation. These include the first 8 items on SUPP05A.
I am unclear how we will use isolated desaturation. Is this meant to refer to a severe apnea, or other acute event such as an airleak?
If so we should probably add a qualifier under other. As a result, my preference would be to include desaturations under other with additional information available. My concern is that when we analyze the data at the end of the trial, we will not know how to interpret the desaturation as a sole reason for intubation/reintubation.
I agree that we have not further specified the degree, length etc of apnea or occurrence and severity of hemodynamic instability, as this would have required agreement and we would not have had adequate documentation of the events.
We have not required detailed recordings to support standard of care decisions that are not related to protocol criteria.
I would favor not adding desaturations for these reasons
Neil Finer

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 8:40 AM
To: Wade Rich; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPP05A

I am sorry but I don not agree with what you have said. When reviewing an infant's chart and determining why he/she may have been intubated or extubated for that matter- I look at the documentation surrounding the event including vital signs, changes in vent. Settings, procedures (blood draws, LP), etc, as well as review notes. I then record the reasons. In fact when looking at the MOP- it really does not give any definitions for apnea, hemodynamic instability either. In a multicentered study I think it is important to have definitions to guide data collection, otherwise everyone adds their own opinion, experiences or ways they do things- and there is no standardization of data collection.....NN

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, June 01, 2006 9:53 AM
To: 'Nancy Newman'; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'

Subject: RE: SUPP05A

All,
The idea of the list of items was to define why the baby was being reintubated. If the clinician is reintubating for desaturations, we do not need a definition. It is their call.
We have never mandated a specific frequency or level of desaturation necessary to choose to reintubate. We just need to be able to recognize at the end of the study the frequency of reintubations which are related to desats. Perhaps rather than defining desats we should make clear that "Yes" should be marked for items which contributed to the decision to re-intubate.
Wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 6:40 AM
To: 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; 'Auman, Jeanette O.'; 'Schaefer, Scott E.'; 'Das, Abhik'
Subject: RE: SUPP05A

Hi- the form looks good and that should work well. We will need a definition of desaturation in the manual.....NN

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, May 31, 2006 6:18 PM
To: Nancy Newman; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: RE: SUPP05A

Sorry, here's the form.
Thanks

From: Zaterka-Baxter, Kristin
Sent: Wednesday, May 31, 2006 6:03 PM
To: 'Nancy Newman'; 'Wade Rich (wrich@ucsd.edu)'; 'nfiner@ucsd.edu'
Cc: 'ellen_hale@oz.ped.emory.edu'; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: SUPP05A

Hi All,
We did not get a chance to discuss this form during the last coordinators conference call (ran out of time). In programming the revision to this form from March, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report.

The attached drafted version of the SUPP05A has been slightly modified so that one 'report' per event would be documented each time it occurred. Each 'report' is actually one half of the paper form. Each time a child is intubated or extubated, Section B will be completed (Section B is now considered one complete report and is not attached to another event). Section A being completed on form SUPP05.

We also added a question about desaturations because it appears to be happening more frequently and if reporting it as 'other' it becomes less clear when analyzing the data. Please let me know any comments, thoughts or suggestions. Once the core group has decided whether or not to incorporate these changes, we can present or discuss it with the rest of the group.

Thanks,
Kris

From:	Zaterka-Baxter, Kristin
To:	Neil Finer; Nancy Newman; Wade Rich; Nancy Newman
Cc:	Schaefer, Scott E.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O.; Petrie, Carolyn; Gantz, Marie
Subject:	RE: SUPP05A
Date:	Thursday, June 01, 2006 2:18:30 PM
Attachments:	SUP09.doc SUPPORT_Manual[Updated06.05.06 uc].doc SUPP05ASafetyMonitor[06.05.06 v2.1(uc)]Rev.doc SUPP11[Rev 06.05.06 uc] .doc

Hi,
Please find attached a drafted technical memo outlining the following revisions to the manual and forms based on discussion during the last coordinators conference call. Please note that the added code on the SUPP11 form has been numbered '9' because code '8' existed in a prior version of this form that was subsequently removed so we can not use code 8 again for different data.

Please also note the revision to Chapter 10 and form SUPP05a was prompted by RTI to program the data entry system to allow cleaner data to be obtained for analysis and supersedes revisions made to this form on 03/07/06 (technical memo #6).

Also attached are the highlighted manual and corresponding forms. Please note that per Dr. Finer's email, we have deleted the question on desaturations in form SUPP05a and this event will continue to be recorded under 'other (specify)'.

Please take a moment and review these documents. We would like to send them out to the rest of the subcommittee to view prior to distribution and activation by the whole group.

Thanks,
Kris

RTI International
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (191) 485-7762
kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 01, 2006 1:04 PM
To: Nancy Newman; Wade Rich; Zaterka-Baxter, Kristin; Nancy Newman
Cc: Schaefer, Scott E.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP05A

Hello Nancy
I appreciate your concerns and your desire to provide specific documentation for events in the trial.
Within the SUPPORT protocol we have criteria for re-intubation for infants randomized to CPAP in the DR, and no such criteria for Control-Surfactant infants. Control-Surfactant infants who are initially extubated are reintubated following unit standard of care.
For CPAP infants we have stated intubation-reintubation criteria that are applicable for 14 days and provide specific conditions/criteria for intubation. These include the first 8 items on SUPP05A.
I am unclear how we will use isolated desaturation. Is this meant to refer to a severe apnea, or other acute event such as an airleak?
If so we should probably add a qualifier under other. As a result, my preference would be to include desaturations under other with additional information available. My concern is that when we analyze the data at the end of the trial, we will not know how to interpret the desaturation as a sole reason for intubation/reintubation.

I agree that we have not further specified the degree, length etc of apnea or occurrence and severity of hemodynamic instability, as this would have required agreement and we would not have had adequate documentation of the events.
We have not required detailed recordings to support standard of care decisions that are not related to protocol criteria.
I would favor not adding desaturations for these reasons
Neil Finer

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 8:40 AM
To: Wade Rich; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPP05A

I am sorry but I don not agree with what you have said. When reviewing an infant's chart and determining why he/she may have been intubated or extubated for that matter- I look at the documentation surrounding the event including vital signs, changes in vent. Settings, procedures (blood draws, LP), etc, as well as review notes. I then record the reasons. In fact when looking at the MOP- it really does not give any definitions for apnea, hemodynamic instability either. In a multicentered study I think it is important to have definitions to guide data collection, otherwise everyone adds their own opinion, experiences or ways they do things- and there is no standardization of data collection.....NN

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, June 01, 2006 9:53 AM
To: 'Nancy Newman'; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPP05A

All,
The idea of the list of items was to define why the baby was being reintubated. If the clinician is reintubating for desaturations, we do not need a definition. It is their call.
We have never mandated a specific frequency or level of desaturation necessary to choose to reintubate. We just need to be able to recognize at the end of the study the frequency of reintubations which are related to desats. Perhaps rather than defining desats we should make clear that "Yes" should be marked for items which contributed to the decision to re-intubate.
Wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 6:40 AM
To: 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; 'Auman, Jeanette O.'; 'Schaefer, Scott E.'; 'Das, Abhik'
Subject: RE: SUPP05A

Hi- the form looks good and that should work well. We will need a definition of desaturation in the manual.....NN

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, May 31, 2006 6:18 PM
To: Nancy Newman; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: RE: SUPP05A

Sorry, here's the form.

Thanks

From: Zaterka-Baxter, Kristin
Sent: Wednesday, May 31, 2006 6:03 PM
To: 'Nancy Newman'; 'Wade Rich (wrich@ucsd.edu)'; 'nfiner@ucsd.edu'
Cc: 'ellen_hale@oz.ped.emory.edu'; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: SUPP05A

Hi All,
We did not get a chance to discuss this form during the last coordinators conference call (ran out of time). In programming the revision to this form from March, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report.

The attached drafted version of the SUPP05A has been slightly modified so that one 'report' per event would be documented each time it occurred. Each 'report' is actually one half of the paper form. Each time a child is intubated or extubated, Section B will be completed (Section B is now considered one complete report and is not attached to another event). Section A being completed on form SUPP05.

We also added a question about desaturations because it appears to be happening more frequently and if reporting it as 'other' it becomes less clear when analyzing the data. Please let me know any comments, thoughts or suggestions. Once the core group has decided whether or not to incorporate these changes, we can present or discuss it with the rest of the group.

Thanks,
Kris

RTI INTERNATIONAL | **Memorandum**

June 5, 2006

SUPPORT TECHNICAL MEMO # 9

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Clarifications to the Manual of Procedures/Forms

The following items have been clarified in the Manual of Procedures:

Chapter 5
Clarification was requested during the April 2006 coordinators conference call regarding manual guidelines for extubation after re-intubation for the control (surfactant) arm. The following underlined text has been added to page 5-4, section 5.1.8 (3) Reintubation:

Control Infants may be reintubated using Standard of Care. Any subsequent extubation will also follow standard practice.

Chapter 10 (Section 10.2.2, page 10-3)
When programming the revision to form SUPP05a per the March 7, 2006 technical memo, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report. Therefore, we have deleted Section C as suggested in March and modified this forms to allow each event to be reported separately.

Please note that this version supersedes the revision in March which was not programmed. This version requests the same data as the previous version dated 10/03/2005 with the addition of a date and time for each event:

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

ADDED: **Report Number**

Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day

Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date

Record the date in which the intubation/extubation occurred.

Section B

Section 10.2.3 (Section C) has been deleted. Highlighted chapter is enclosed.

Form SUPP05a *has been revised to reflect this revision (version 2.1; dated 06/05/06). Highlighted form enclosed*

Chapter 16
A request was made during the May 2006 coordinators conference call to add a code identifying infants who are in no support all day and off the study oximeter for any days between day 15 through 36 weeks. The following underlined text has been added to page 16-1, section 16.1.1 (bullet 3):

Highest Level of Support
Record the highest level of support the infant is in at the scheduled time points during this STUDY day.
Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
7= No Support, 9= No Support all day and off the study oximeter*.

* Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.

Form Supp11 *has been modified to include Code 9 (version 2.1; dated 06/05/06).*

The updated Manual of Procedures and forms SUPP05a and SUPP11 have been posted on the Neonatal Web site with the revision date of 06/05/06.

cc: Rosemary Higgins

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
Revised June 27, 2005
Revised October 3, 2005
Revised March 7, 2006
Revised March 23, 2006
Revised June 5, 2006

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.

Respiratory Support After 14 Days (SUPP11)
This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

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 ≥ 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. **Any subsequent extubations will also follow standard practice.**

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 <u>No</u> 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 $Sa0_2$ ≥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
SUPP05 and SUPP05A

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

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 results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**

Note that the FiO2 corresponding with the ABG measurements will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

For blood gas information record the actual 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 8:00 the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. 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.

For all other time points enter the FiO_2 and Mode of Support.

c. pH

Record the acid base status of the blood.

d. $C0_2$

e. PO_2:

f. FiO_2

Record the **FiO_2** at the time the blood gas was collected or at other scheduled time points.

g. Source:

Record the source of the blood gas

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

i. If Mode =5 record Flow Rate

Record the flow rate for infants on nasal cannula

4. If Mode of Support =4 (CPAP), type used:

Record the type of CPAP

2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

13. Oximeter Alarm Check.

The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine.

The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

14. 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

15. Was the infant intubated or extubated on this day?
If Yes, Complete Section B and/or Section C of the SUPP05A

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs complete Section B for each event. ~~in one day, complete Section C.~~ Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

Report Number
Consecutively number each event as reported on Section B of the SUPP05a form.

1. Study Day
Record the study day (1 – 14) in which the intubation/extubation occurred in MM/DD/YYYY format

2. Date
Record the date in which the intubation/extubation occurred.

Section B

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 information prior to intubation:
Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record ""*
Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code ""*
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. **Desaturation?** Record Yes if the infant experienced desaturations requiring intubation on this day
~~9.~~ 10. **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
4. Saturation

~~**10.2.3 Section C. Intubation/Extubation Information (For NICU ONLY)**~~
~~**If more than one intubation/extubation occurs in one day, complete Section C.**~~
~~Record the intubation/extubation history for each Study Day 1–14.~~
~~**1. Did the infant have more than one intubation/extubation on this day?**~~
~~**If Yes,**~~
~~**2. 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 information prior to intubation:~~
~~*Record the blood gas that, in the opinion of the investigator, is most associated with the event. If there is no blood gas measurement associated with this event, record "*"*~~
~~*Example: If an infant is stable and then requires emergent intubation and a blood gas was not obtained, code "*"*~~
~~**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.

3. 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

4. Saturation

NOTE: If more than two intubations/extubations were performed, complete additional SUPP05A, Section C for this study day.

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 Kris Zaterka-Baxter 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 or 4b is a partial retinal detachment
   - Code 5 = stage 5 which is a total retinal detachment
   - Code 6 = Post laser/cyro (do not use stages)
   - Code 9 = Old scars, but no active ROP

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

- Vessel growth if mature to the ora serrata in all clock hours
- Vessels in zone III for two sequential eye examinations (i.e. two examinations in a row)

Unfavorable

- type I threshold ROP
- Laser (or cryo or both) surgery for acute ROP
- retinal detachment stage 5
- retinal detachment stage 4b

Other

- 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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood,
  7= No Support, 9= **No Support all day and off the study oximeter***.

  *** Code 9 should be recorded in the 0600 time period for each day the infant is in no support and is not on the study oximeter. Oxygen (b), flow rate (c), and oximeter alarm check (d) are not required for this time point. No further data are required for the following time points on this day.**

- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes). Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time-during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the

infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.

- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 17

OXIMETER SETUP

17.1 Oximeter Setup – Masimo Radical

Review the following EACH TIME the oximeter is placed on a baby.

17.1.1 Power

If possible, units should remain plugged in between uses. Where this is not possible the oximeter should be plugged in as soon as possible after randomization.

17.1.2 Initial Settings – [Radical Manual pp. 30-42]

Date – Check to see that the date and time are correct. This must be done prior to gathering data. **Changing the date or time after data collection has started will erase the memory!**

Sensitivity – Set to Normal Mode
Averaging Time – Set to 16 seconds
Alarm Limits – Sat: Suggested between 85 and 95.
Audible Delay – 10 seconds
Trend Period – [43-45] - 10 Seconds **Note: Changing this setting during a recording will erase all data !!**

17.1.3 Help – If you can not find these settings using your oximeter manual, or if you have any problems with the Masimo masked oximeters used in the SUPPORT study, please contact:

1. The local Masimo Clinical Specialist who did the inservicing for your center
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter.

   and/or

2. Masimo Technical Support at 800-326-4890, option 2. tech@Masimo.com
   Please identify yourself as one of the SUPPORT centers, with questions about a masked oximeter. The techs are aware of SUPPORT and the masked oximeters.

   and/or

3. Dr Maribeth Sayre, Director of Medical Affairs for Masimo, and the Masimo liaison for the SUPPORT study. Her contact information is: msayre@Masimo.com
   cell phone 925-337-(b) [redacted]

If a masked oximeter is malfunctioning, it must be sent back to Masimo headquarters. First, a RMA # (Return Material Authorization number) is needed. A copy of the form **is**

contained in Appendix E. . Please identify the facility as one of the SUPPORT centers, and the product as a masked Radical handheld or docking station.

If there are questions relating to alarm parameters, they should be referred to Wade Rich.

PLEASE COPY DR. MARIBETH SAYRE ON ALL EMAILS RELATED TO THE MASKED OXIMETERS.

17.2 Downloading Data

17.2.1 Software

The software used to download the data is called TExtract. If you have not gotten a copy, it is available by email from wrich@ucsd.edu or it can be downloaded to your Network computer by RTI.

Using TExtract
A powerpoint presentation showing how to use TExtract is included in the manual as Appendix D.

17.2.2 Cable

Data may be downloaded from the oximeter to a laptop using either a serial cable or a USB-to-Serial cable. A picture of a USB-Serial cable is included in the power-point presentation that was sent out to all the sites.

17.2.3 Preparing Masimo for Download

- Turn Oximeter on.
- Output should be Binary
- Select button
- Use arrow key to highlight "Output".
- Select button.
- Enter the Serial Menu by selecting the button.
- Use arrow key to select "Binary".
- Select ☑ button.
- Select ☒ button twice.

When to Download
Downloads should be done every 2 weeks, or earlier if a child reaches a study milestone (e.g. Off oxygen for 72 hrs, death, discharge, or 36 weeks PCA)

17.2.4 After the download:

Be sure to clear the memory of the Masimo after you have downloaded the data. Otherwise you will send RTI data which they already have along with the new data the next time you download. Clearing the memory is done as follows:

From the main screen when the Masimo is first turned on:
Select the → button.
Select the button.

Select the  button twice.
Select the 🗑 icon.
Select the ☑ icon and the data will be dumped.

17.2.5 Uploading Data to Network Computer

Data can be transferred from the laptop to the network computer by way of a floppy disk or a USB Memory Stick. The USB device is preferable because it will hold many studies instead of just one.

To upload this data to your Network computer the USB stick must be put into the USB port on the computer. This is often in the back. A USB extension cable will help make this easier, as one end can just be placed on the desk for easy reach.

The SUPPORT data entry software program from RTI will take you through the process of uploading. The information regarding how to label the files is included in the TExtract Power point appendix D to this manual.

17.2.6 Masimo Technical Issues

It is recommended that the Radical Handheld be docked to the docking station and attached to an AC power source when it is not in use to ensure that the battery remains fully charged. All batteries lose capacity with age. When battery run time is significantly reduced, it is advisable to completely discharge and fully recharge the battery pack. Masimo does not give a recommended TIME FRAME for performing a discharge cycle since every environment is different.

17.2.7 How to Deep-Discharge the Radical Battery

The discharge cycle will take approximately 16 hours to complete for the handheld battery. The Docking Station battery will take approximately 30 hours to complete. A message will appear in the service screen when the discharge cycle is complete. The batteries will be fully charged after completion of the cycle.

Note: *In order for the discharge cycle to be properly completed, the Handheld must be docked to a Docking Station and supplied with AC power throughout the cycle.*

Warning: WHEN DEEP-DISCHARGING THE HANDHELD OR DOCKING STATION BATTERY, MAKE SURE THAT THE DEVICE HAS BEEN REMOVED FROM SERVICE UNTIL FULL BATTERY CAPABILITY CAN BE RESTORED.

1. Press the three page button to access the main menu screen
2. Highlight the Service menu and press the single page button
3. Enter password 2 – 3 – 1
4. Press single page button
5. Confirm by pressing the checkmark
6. Wait until message of "Discharge Cycle is Complete"

17.2.8 Defective Equipment

If you need to return defective Masimo equipment, please contact Technical Support at Masimo 1-800-326-4890 for a Return Merchandise Authorization #.
You will need the device serial # when you call.

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

_____

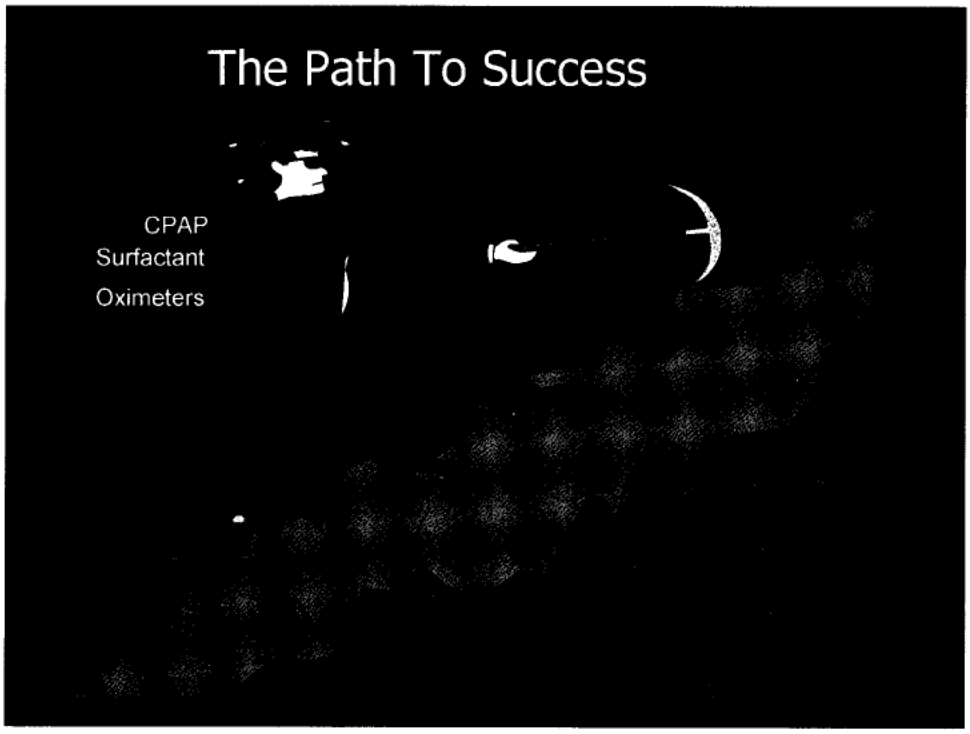
Signature of person explaining and getting consent DATE

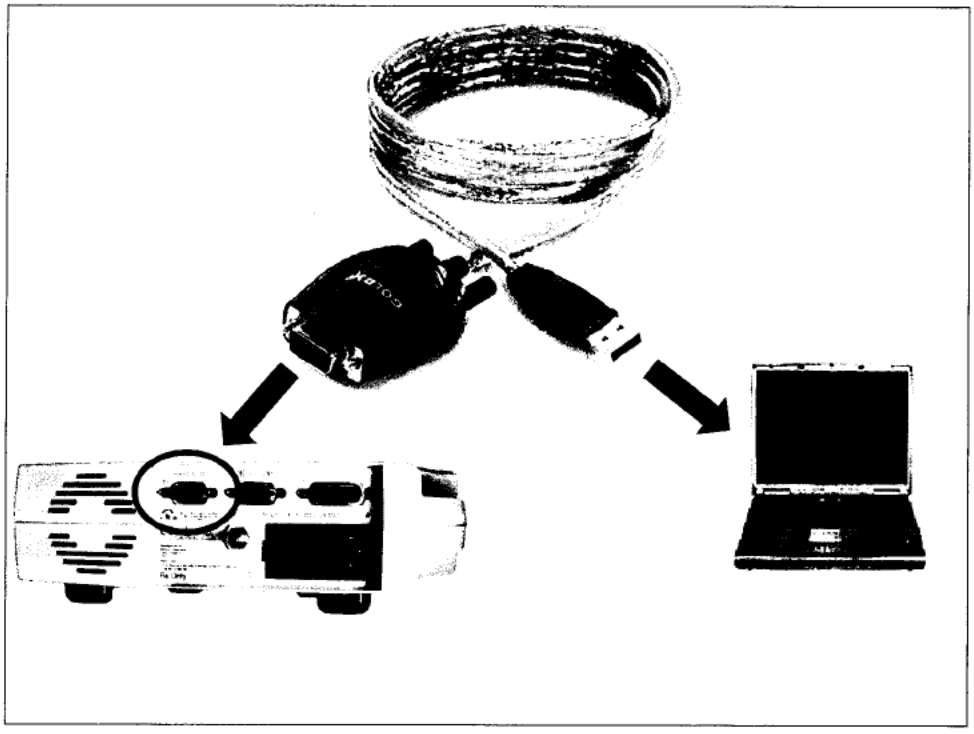
APPENDIX C

PHYSIOLOGIC DEFINITION OF BRONCHOPULMONARY DYSPLASIA (Refer to Stand Alone Protocol, Manual of Operations and Forms)

APPENDIX D

SUPPORT DOWN LOAD





Turn Oximeter on.

Select button.

Use arrow key to highlight "Output".

Select button.

Enter the Serial Menu by selecting the button.

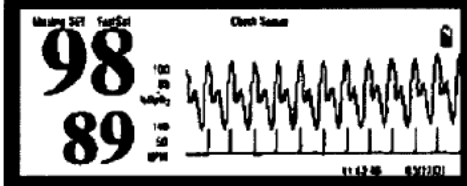
Use arrow key to select "Binary".

Select button.

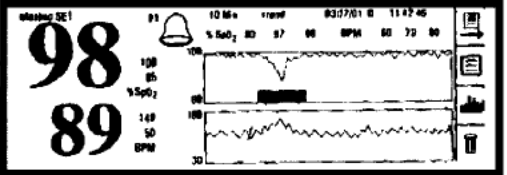
Select button twice.

Quick Reference on Masimo Extraction Utility
Masimo Unit Setup:

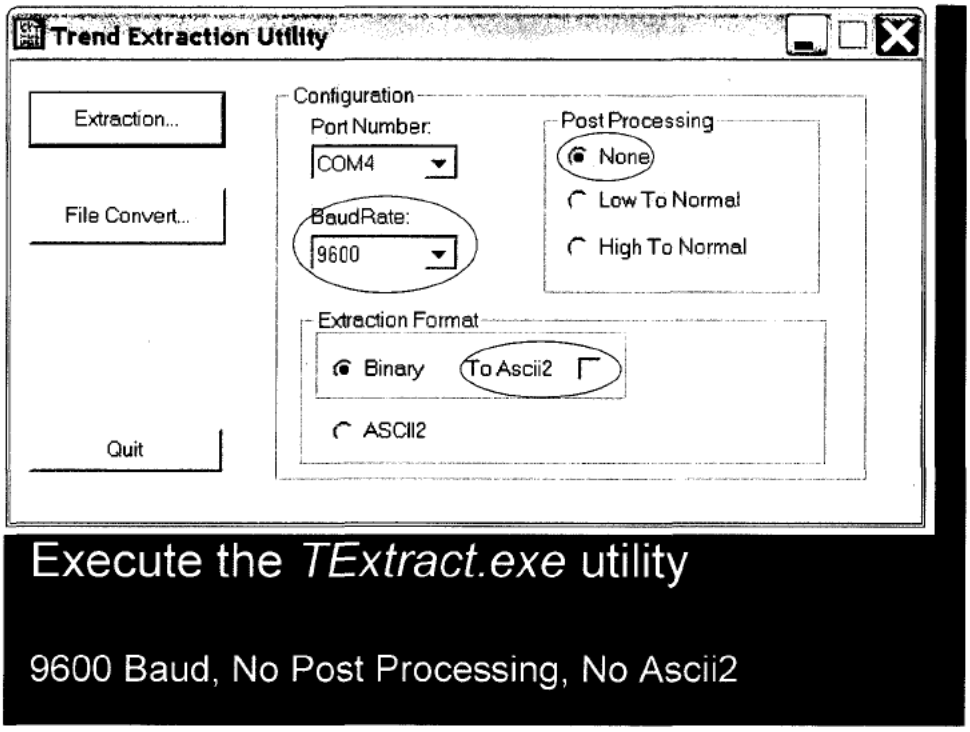
Make sure the Radical is in run mode and not in mode.



YES

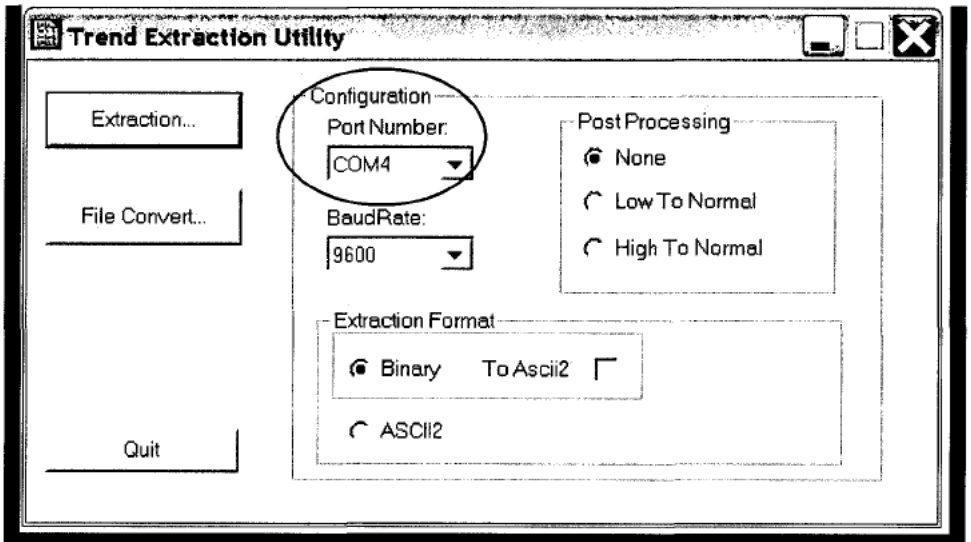


No

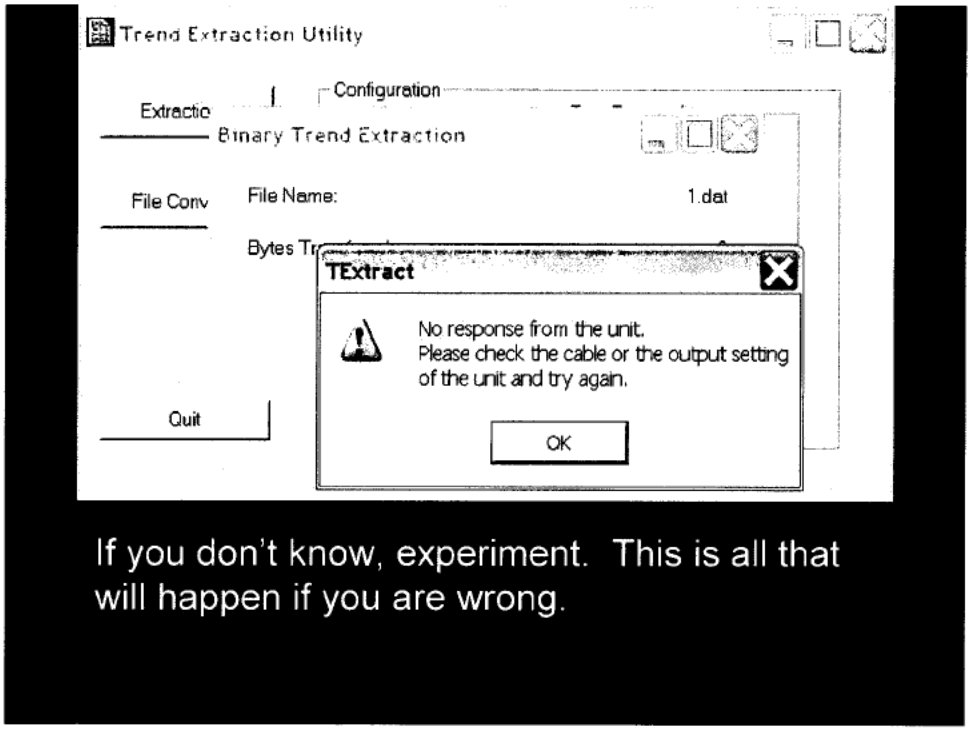


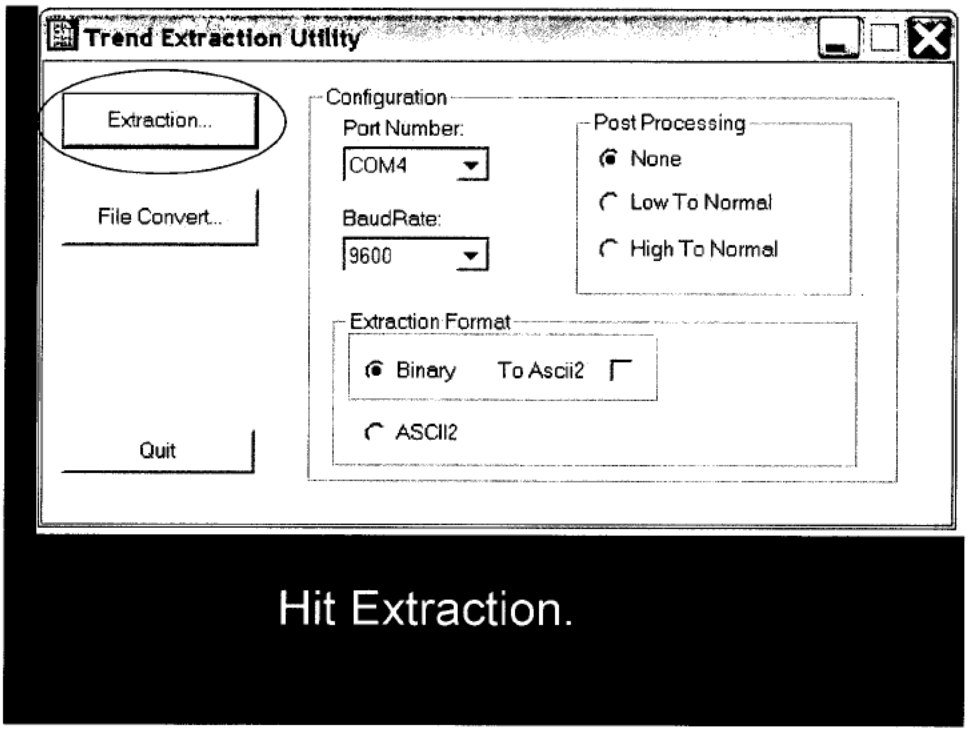
Execute the *TExtract.exe* utility

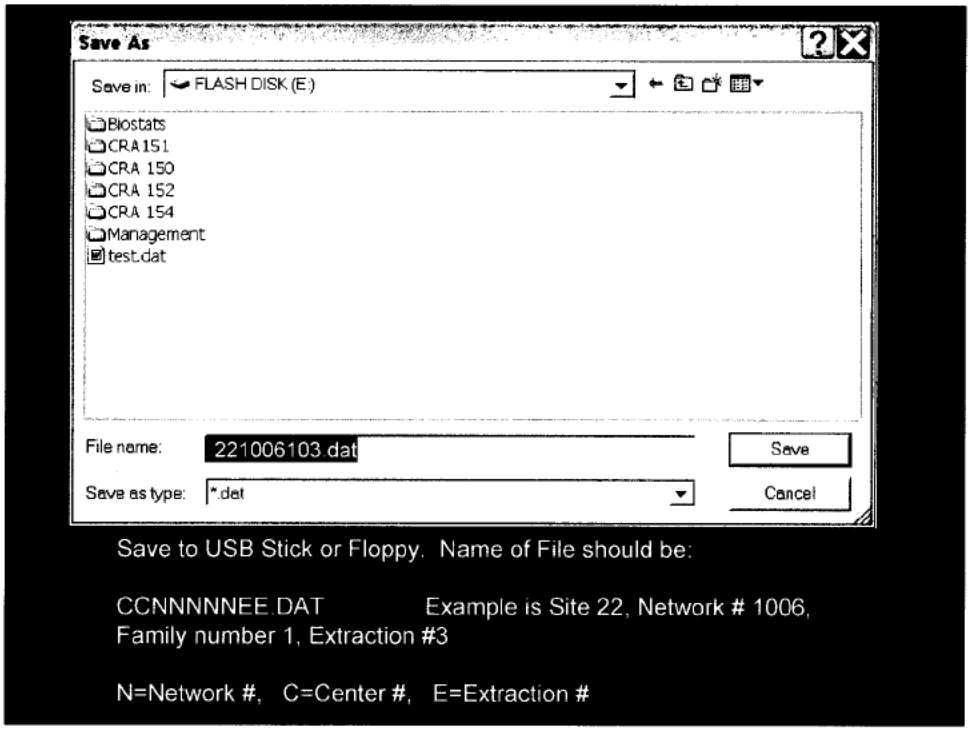
9600 Baud, No Post Processing, No Ascii2

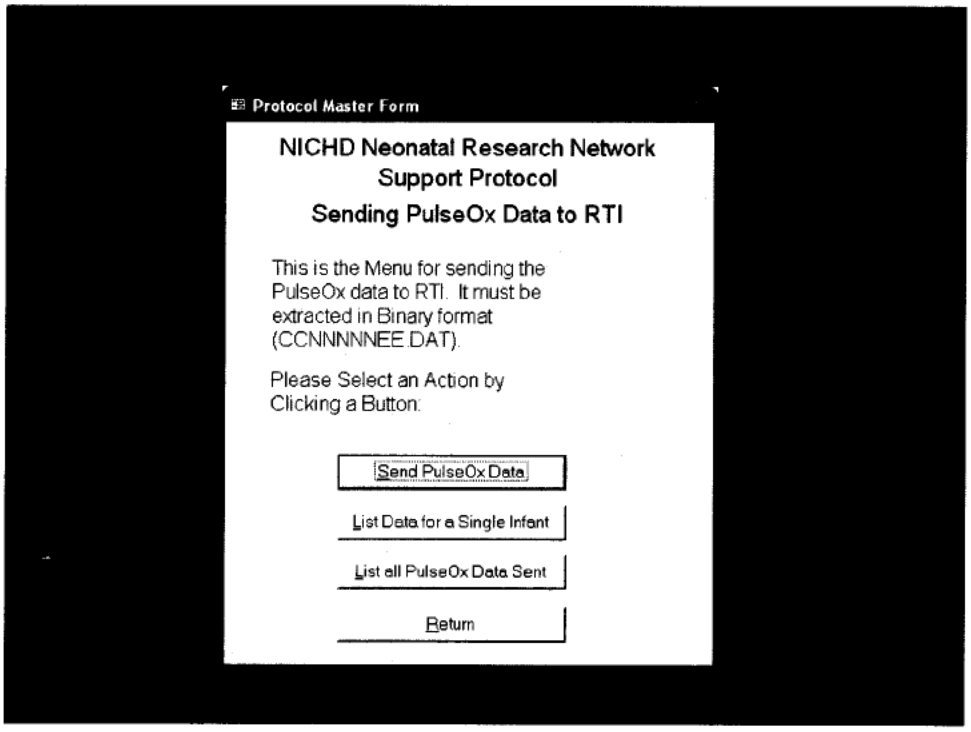


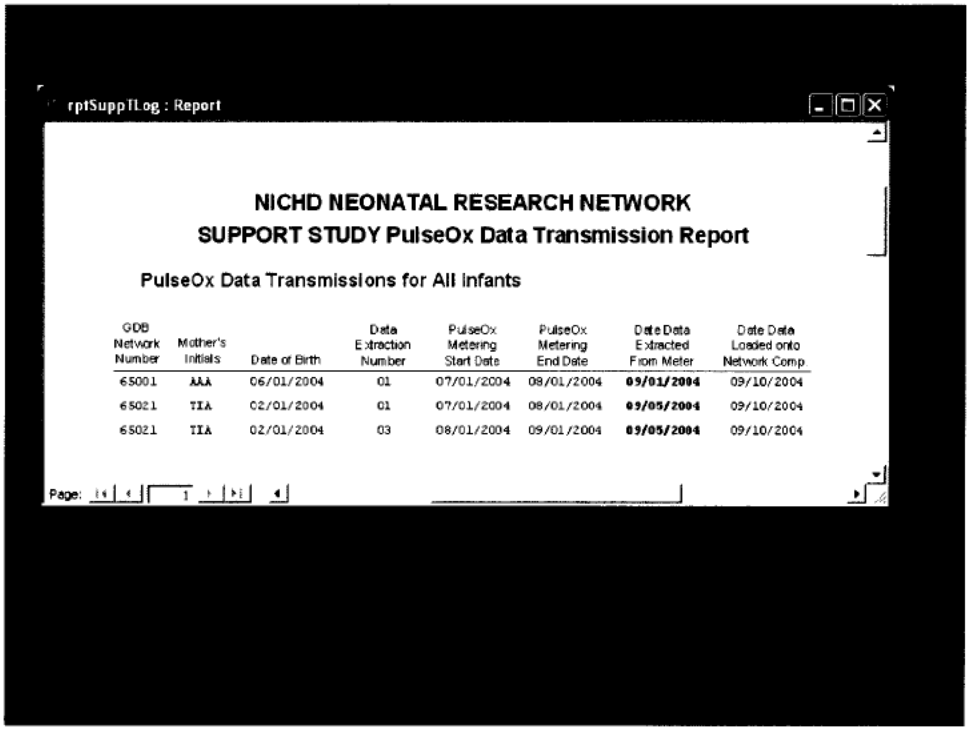
In the "*Configuration*" panel, select the COM port that is currently connected to the Radical unit.

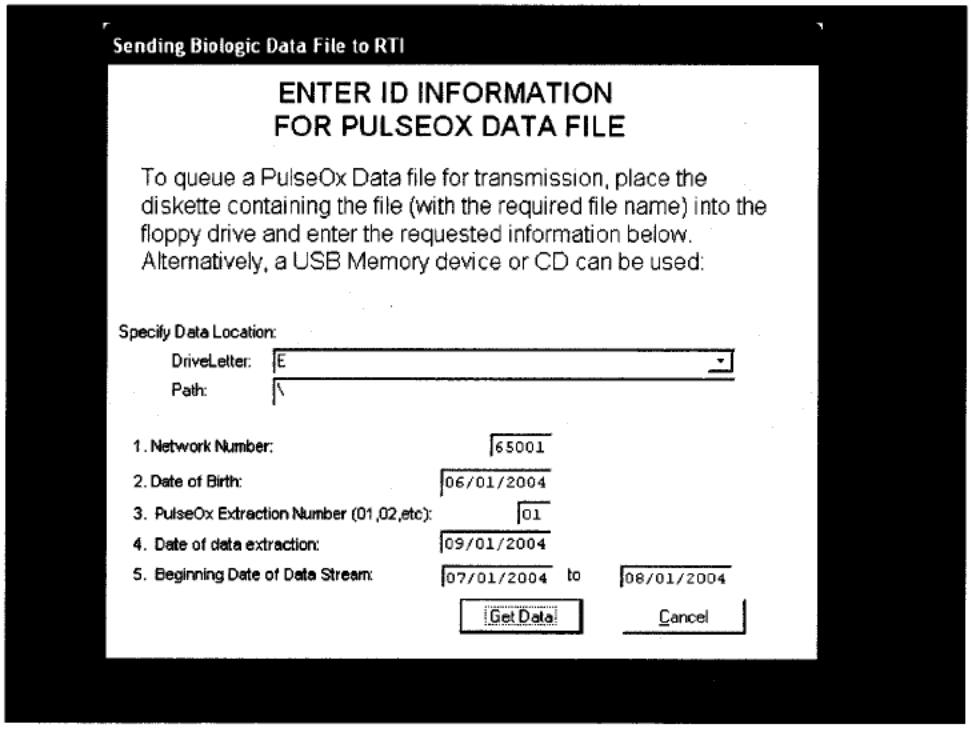


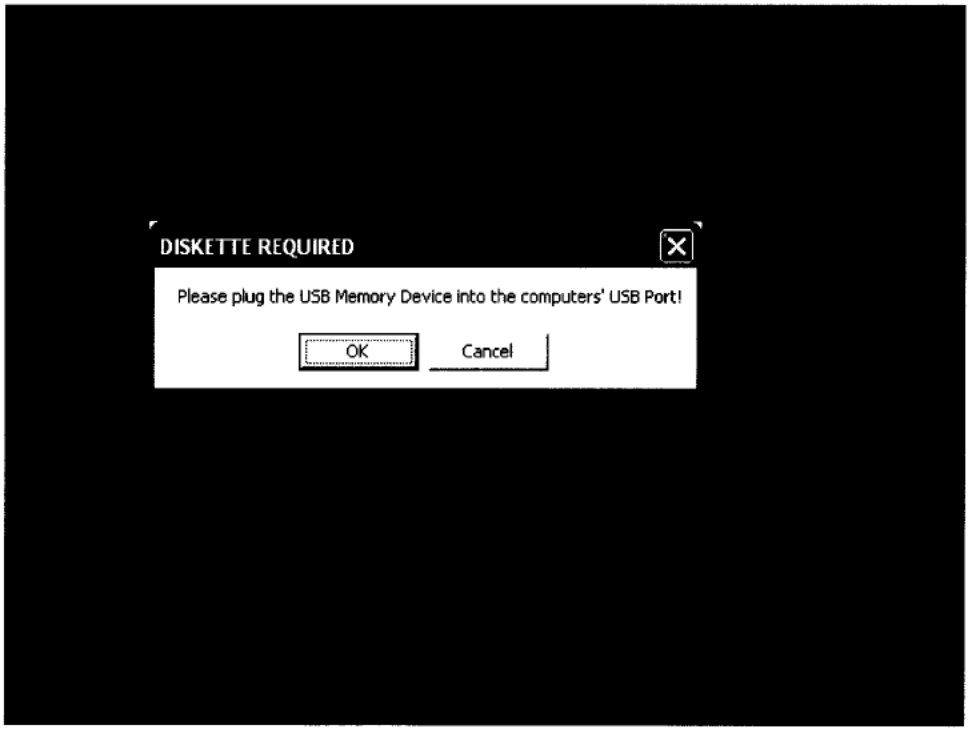


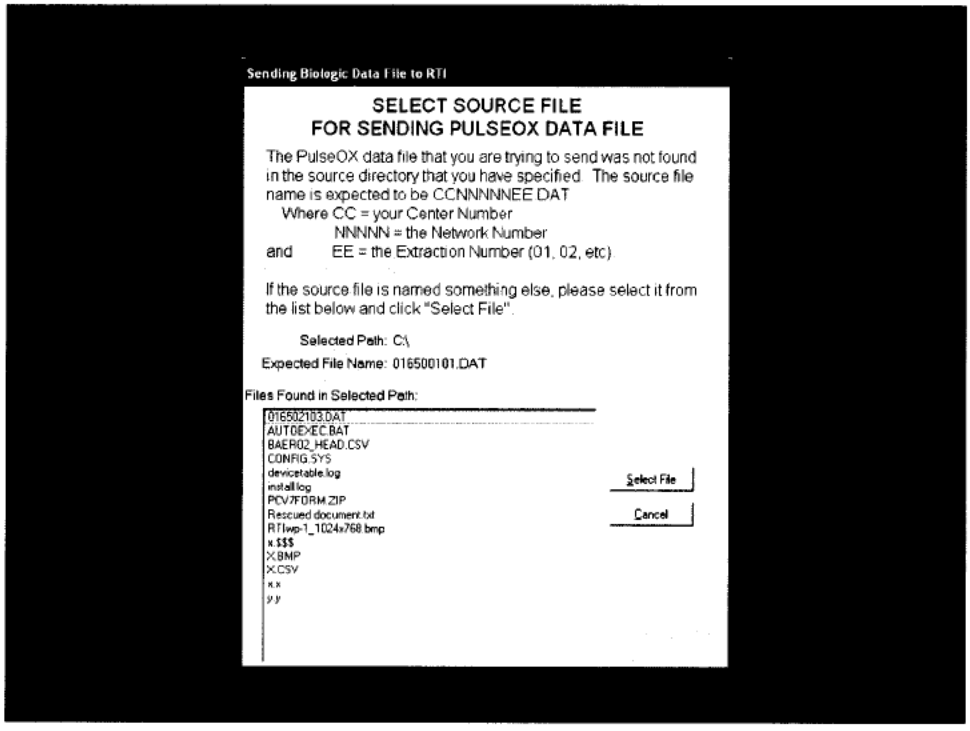


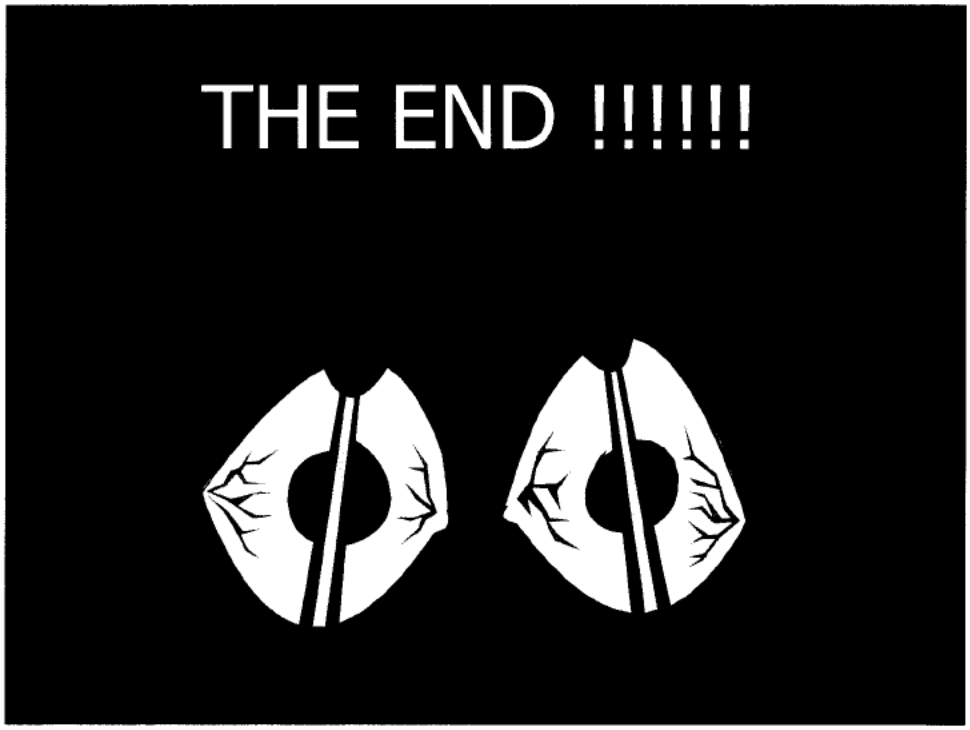












APPENDIX E

RETURN MATERIAL AUTHORIZATION FORM (RMA)

SHIP TO:

MASIMO®

40 Parker
Irvine, CA 92618 USA
Tel: 1 800 326-4890
Fax: 949-297-7499
Email tech@masimo.com

RETURNED **M**ATERIAL **A**UTHORIZATION

 # xxxx

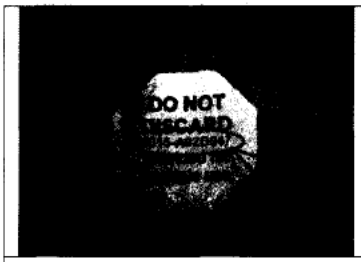
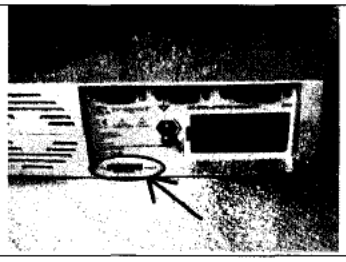
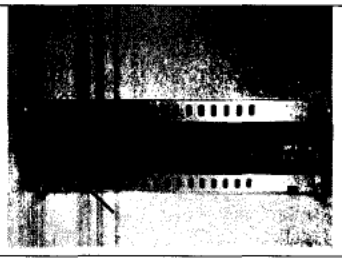
PLEASE ENSURE ALL RETURNED PRODUCTS ARE BIO HAZARD CLEANED

1. Complete this form.
2. Return this form with the product by affixing to the outside of the container with a clear shipper.

THANK YOU!

FACILITY NAME				
RETURN SHIP TO ADDRESS				
PHONE NUMBER				
FAX NUMBER				
EMAIL ADDRESS				
PO NUMBER				
CONTACT NAME				
DEPARTMENT				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				
PRODUCT				
SERIAL/LOT #				
DISCREPANCY				

How to locate the Serial or Lot number

			
Sensors & Cables (On DO NOT DISCARD label on cable)	**Radical™ Handheld (On rear of unit)**	**Radical™ Docking Station (On rear of unit)**	**Rad-9™ (On rear of unit)**

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen.

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
   (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SUPPORT Rel 3.0
Revised June 5, 2006

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

This form should be completed if more than one intubation/extubation occurs in the same day.

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

Report No __ __

1. Study Day: __ __ **2. Date: __ __ / __ __ / __ __ __ __**

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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: __ __ __

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	15 __ __/__ __/__ __ __ __ Month Day Year	16 __ __/__ __/__ __ __ __ Month Day Year	17 __ __/__ __/__ __ __ __ Month Day Year	18 __ __/__ __/__ __ __ __ Month Day Year	19 __ __/__ __/__ __ __ __ Month Day Year	20 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	21 __ __/__ __/__ __ __ __ Month Day Year	22 __ __/__ __/__ __ __ __ Month Day Year	23 __ __/__ __/__ __ __ __ Month Day Year	24 __ __/__ __/__ __ __ __ Month Day Year	25 __ __/__ __/__ __ __ __ Month Day Year	26 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	27 ___/___/_____ Month Day Year	28 ___/___/_____ Month Day Year	29 ___/___/_____ Month Day Year	30 ___/___/_____ Month Day Year	31 ___/___/_____ Month Day Year	32 ___/___/_____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	33 __/__/__ Month Day Year	34 __/__/__ Month Day Year	35 __/__/__ Month Day Year	36 __/__/__ Month Day Year	37 __/__/__ Month Day Year	38 __/__/__ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: _ _ _ _ _ Birth No: ___ Mother's Initials: _ _ _

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___ / ___ / _ _ _ _

Study Day	39 __ __/__ __/__ __ __ __ Month Day Year	40 __ __/__ __/__ __ __ __ Month Day Year	41 __ __/__ __/__ __ __ __ Month Day Year	42 __ __/__ __/__ __ __ __ Month Day Year	43 __ __/__ __/__ __ __ __ Month Day Year	44 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	45 ___/___/_____ Month Day Year	46 ___/___/_____ Month Day Year	47 ___/___/_____ Month Day Year	48 ___/___/_____ Month Day Year	49 ___/___/_____ Month Day Year	50 ___/___/_____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: ___

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ____/____/____

Study Day	51	52	53	54	55	56
	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/_____

Study Day	57	58	59	60	61	62
	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	63 __ __/__ __/__ __ __ __ Month Day Year	64 __ __/__ __/__ __ __ __ Month Day Year	65 __ __/__ __/__ __ __ __ Month Day Year	66 __ __/__ __/__ __ __ __ Month Day Year	67 __ __/__ __/__ __ __ __ Month Day Year	68 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

RESPIRATORY SUPPORT AFTER 14 DAYS

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: _ _ Site No: _ _ Network No: _ _ _ _ _ Birth No: _ _ Mother's Initials: _ _ _

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks _ _ / _ _ / _ _ _ _

Study Day	69	70	71	72	73	74
	_ _ / _ _ / _ _ _ _ Month Day Year	_ _ / _ _ / _ _ _ _ Month Day Year	_ _ / _ _ / _ _ _ _ Month Day Year	_ _ / _ _ / _ _ _ _ Month Day Year	_ _ / _ _ / _ _ _ _ Month Day Year	_ _ / _ _ / _ _ _ _ Month Day Year
1. Scheduled Time: 06:00	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.
(d) Oximeter Alarm Check	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _
2. Scheduled Time: 12:00	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.
(d) Oximeter Alarm Check	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _
3. Scheduled Time: 18:00	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.
(d) Oximeter Alarm Check	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _
4. Scheduled Time: 23:59	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)	_ _ : _ _ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.	_ _ . _ _ _ Liters/Min.
(d) Oximeter Alarm Check	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _	_ _ : _ _

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	75 __ __/__ __/__ __ __ __ Month Day Year	76 __ __/__ __/__ __ __ __ Month Day Year	77 __ __/__ __/__ __ __ __ Month Day Year	78 __ __/__ __/__ __ __ __ Month Day Year	79 __ __/__ __/__ __ __ __ Month Day Year	80 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

RESPIRATORY SUPPORT AFTER 14 DAYS

**Mode	1= HFV	2= CV	3= Nasal SIMV	4= CPAP	5= NC	6=Hood	7= No Support	9= No Support all day and not on study oximeter

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	81 __ __/__ __/__ __ __ __ Month Day Year	82 __ __/__ __/__ __ __ __ Month Day Year	83 __ __/__ __/__ __ __ __ Month Day Year	84 __ __/__ __/__ __ __ __ Month Day Year	85 __ __/__ __/__ __ __ __ Month Day Year	86 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support 9= No Support all day and not on study oximeter

From: Neil Finer
To: Nancy Newman
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP05A
Date: Thursday, June 01, 2006 1:59:56 PM

Hi Nancy
I definitely appreciate your perspective, and I know that you are very thoughtful.
I am only trying to imagine how we might use the information that we are collecting.
I always enjoy your views.
Be well
Neil

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 10:36 AM
To: Neil Finer
Subject: RE: SUPP05A

Hi Neil- that's fine with me not to add desats as a separate item—I did not add this in the revision. In fact I have used this as an other as a reason for re-intubation. I also understand your concern for the definition issues. I do feel though, that there is always decision making when collecting data because the documentation is not always as good as you hope it to be. And the people collecting the data may need to interpret what is going on.....NN

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 01, 2006 1:04 PM
To: Nancy Newman; Wade Rich; Zaterka-Baxter, Kristin; Nancy Newman
Cc: Schaefer, Scott E.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPP05A

Hello Nancy
I appreciate your concerns and your desire to provide specific documentation for events in the trial.
Within the SUPPORT protocol we have criteria for re-intubation for infants randomized to CPAP in the DR, and no such criteria for Control-Surfactant infants. Control-Surfactant infants who are initially extubated are reintubated following unit standard of care.
For CPAP infants we have stated intubation-reintubation criteria that are applicable for 14 days and provide specific conditions/criteria for intubation. These include the first 8 items on SUPP05A.
I am unclear how we will use isolated desaturation. Is this meant to refer to a severe apnea, or other acute event such as an airleak?
If so we should probably add a qualifier under other. As a result, my preference would be to include desaturations under other with additional information available. My concern is that when we analyze the data at the end of the trial, we will not know how to interpret the desaturation as a sole reason for intubation/reintubation.
I agree that we have not further specified the degree, length etc of apnea or occurrence and severity of hemodynamic instability, as this would have required agreement and we would not have had adequate documentation of the events.
We have not required detailed recordings to support standard of care decisions that are not related to protocol criteria.
I would favor not adding desaturations for these reasons
Neil Finer

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 8:40 AM

To: Wade Rich; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPP05A

I am sorry but I don not agree with what you have said. When reviewing an infant's chart and determining why he/she may have been intubated or extubated for that matter- I look at the documentation surrounding the event including vital signs, changes in vent. Settings, procedures (blood draws, LP), etc, as well as review notes. I then record the reasons. In fact when looking at the MOP- it really does not give any definitions for apnea, hemodynamic instability either. In a multicentered study I think it is important to have definitions to guide data collection, otherwise everyone adds their own opinion, experiences or ways they do things- and there is no standardization of data collection.....NN

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, June 01, 2006 9:53 AM
To: 'Nancy Newman'; 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; Neil Finer
Cc: 'Schaefer, Scott E.'; 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: SUPP05A

All,
The idea of the list of items was to define why the baby was being reintubated. If the clinician is reintubating for desaturations, we do not need a definition. It is their call.
We have never mandated a specific frequency or level of desaturation necessary to choose to reintubate. We just need to be able to recognize at the end of the study the frequency of reintubations which are related to desats. Perhaps rather than defining desats we should make clear that "Yes" should be marked for items which contributed to the decision to re-intubate.
Wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Thursday, June 01, 2006 6:40 AM
To: 'Zaterka-Baxter, Kristin'; 'Nancy Newman'; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; 'Auman, Jeanette O.'; 'Schaefer, Scott E.'; 'Das, Abhik'
Subject: RE: SUPP05A

Hi- the form looks good and that should work well. We will need a definition of desaturation in the manual.....NN

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Wednesday, May 31, 2006 6:18 PM
To: Nancy Newman; wrich@ucsd.edu; nfiner@ucsd.edu
Cc: ellen_hale@oz.ped.emory.edu; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: RE: SUPP05A

Sorry, here's the form.
Thanks

From: Zaterka-Baxter, Kristin
Sent: Wednesday, May 31, 2006 6:03 PM
To: 'Nancy Newman'; 'Wade Rich (wrich@ucsd.edu)'; 'nfiner@ucsd.edu'
Cc: 'ellen_hale@oz.ped.emory.edu'; Auman, Jeanette O.; Schaefer, Scott E.; Das, Abhik
Subject: SUPP05A

Hi All,
We did not get a chance to discuss this form during the last coordinators conference call (ran out of time).

In programming the revision to this form from March, it was suggested that one 'report' for each intubation or extubation in the DE system would be cleaner data to analyze instead of having 2 sections (or more than one event) per report.

The attached drafted version of the SUPP05A has been slightly modified so that one 'report' per event would be documented each time it occurred. Each 'report' is actually one half of the paper form. Each time a child is intubated or extubated, Section B will be completed (Section B is now considered one complete report and is not attached to another event). Section A being completed on form SUPP05.

We also added a question about desaturations because it appears to be happening more frequently and if reporting it as 'other' it becomes less clear when analyzing the data. Please let me know any comments, thoughts or suggestions. Once the core group has decided whether or not to incorporate these changes, we can present or discuss it with the rest of the group.

Thanks,
Kris

From: Brenda Poindexter
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, May 31, 2006 3:40:02 PM

Thanks Rose - I wish Lucy had asked me first before bothering you and Wade....I could have told her it would be fine to enroll the others. Fortunately, the mom has stopped contracting (for now) after delivering (b) (6) somewhat precipitously. Brenda

> Brenda
> A question came earlier today about possible enrollment of infants from a (b) (6) for which one baby has delivered. If you can obtain
> consent, the remaining (b) (6) can be enrolled. I think that Wade was
> getting back to Lucy on this.
> Thanks and thanks to Lucy for asking!! Every baby counts!
> Rose
> ----------
> Sent from my BlackBerry Wireless Handheld

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, May 31, 2006 1:19:53 PM

Agree
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 31, 2006 9:49 AM
To: Wade Rich; Das, Abhik
Cc: Schaefer, Scott E.; Neil Finer
Subject: RE: SUPPORT

I think this is fine. There are cases of multiples being born on different days – they get coded as (b) (6) but only [redacted] would be enrolled.

Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, May 31, 2006 12:49 PM
To: 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Schaefer, Scott E.'; Neil Finer
Subject: RE: SUPPORT

Abhik, Scott,

We would love to have these babies. Does this work for you in terms of data collection and statistical integrity?

Wade

From: Miller, Lucy C. [mailto:lucmille@iupui.edu]
Sent: Wednesday, May 31, 2006 9:43 AM
To: wrich@ucsd.edu
Subject: SUPPORT
Importance: High

Wade,
I have another question…we have a Mom that came in this morning with (b) (6) . She delivered (b) (6) prior to our neonatal consult (which I need to have happen prior to approaching her about consent). They have been able to stop her labor and the baby's membranes are intact and have quieted down. Can I approach her for consent for (b) (6) ?
Thanks,
Lucy

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Cc: Schaefer, Scott E.; Neil Finer; Poole, W. Kenneth; Gantz, Marie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT
Date: Wednesday, May 31, 2006 12:49:53 PM

Should be fine.
Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 31, 2006 12:49 PM
To: wrich@ucsd.edu; Das, Abhik
Cc: Schaefer, Scott E.; Neil Finer
Subject: RE: SUPPORT

I think this is fine. There are cases of multiples being born on different days – they get coded as t(b) (6) but only [redacted] would be enrolled.

Rose

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, May 31, 2006 12:49 PM
To: 'Das, Abhik'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Schaefer, Scott E.'; Neil Finer
Subject: RE: SUPPORT

Abhik, Scott,

We would love to have these babies. Does this work for you in terms of data collection and statistical integrity?

Wade

From: Miller, Lucy C. [mailto:lucmille@iupui.edu]
Sent: Wednesday, May 31, 2006 9:43 AM
To: wrich@ucsd.edu
Subject: SUPPORT
Importance: High

Wade,
I have another question...we have a Mom that came in this morning with (b) (6) [redacted]. She delivered (b) (6) [redacted] prior to our neonatal consult (which I need to have happen prior to approaching her about consent). They have been able to stop her labor and the baby's membranes are intact and have quieted down. Can I approach her for consen(b) (6) [redacted]?
Thanks,
Lucy

From: Frantz, Ivan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Coordinator SUPPORT Protocol
Date: Thursday, May 25, 2006 2:00:41 PM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 17, 2006 10:30 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Cc: Zaterka-Baxter, Kristin; Neil Finer; Carolyn Petrie; Kathy J Auten; Wade Rich; Angelita Hensman
Subject: Coordinator SUPPORT Protocol

Hi,
The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007. They are asking that research proposals be submitted by June 30 for next year's meeting. **The submission would consist of the design of the protocol**.

The link to the ACRP home page is <http://www.acrpnet.org/> for your reference.

Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.

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

****

Confidentiality Notice

****

From: Wade Rich
To: "Nancy Newman"
Cc: "Michele Walsh"; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"
Subject: RE:
Date: Tuesday, May 23, 2006 10:47:09 AM

I am not sure how the two protocols relate. We are getting data every 2 hours. If a child is on oxygen for a feeding, and we count that two hour block as being on oxygen, we are as close to telling the truth as if we said he was on room air the whole time. It is a best guess in either case. Changing it at this point would have little effect. We have far bigger blocks of undefined time because of the blood gas timing issue than we will with feeds. It is obviously up to you guys, but I do not see that the error is worth the extra work in changing an MOP at 25% enrollment.
wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, May 23, 2006 7:32 AM
To: wrich@ucsd.edu
Subject: RE:

These are two different situations- and are used separately in the Physio Def and I think need to be used likewise in SUPPORT.

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 23, 2006 10:27 AM
To: 'Nancy Newman'
Subject: RE:

It is a temporary oxygen increase. That was the intent. Add it if you think it is not clear.
wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, May 23, 2006 7:21 AM
To: wrich@ucsd.edu
Subject: RE:

THIS DOES NOT MENTION THE INFANT WHO IS ONLY RECEIVING OXYGEN OR FLOW WITH FEEDS.

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, May 23, 2006 10:20 AM
To: 'Nancy Newman'; Neil Finer
Cc: 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Zaterka-Baxter, Kristin'
Subject: RE:

We do. This is page 16-1.

wade

Oxygen -Yes/No

Record "Yes" if the infant was on oxygen at any time during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (= 30 minutes). Record "No" if the infant is not in oxygen on this day.

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, May 23, 2006 6:57 AM
To: nfiner@ucsd.edu
Cc: 'Michele Walsh'; 'Higgins, Rosemary (NIH/NICHD) [E]'; wrich@ucsd.edu; 'Zaterka-Baxter, Kristin'
Subject:

Hi, as we are filling out lots of SUPPORT forms- it came up that on the SUPP11 form-(respiratory support after 14 days to 36 wks)- there may be infants who have oxygen and/or flow rate only with feeds. And if this falls at the specified time points it will appear that the infant is requiring this support when it could be only with feeds. It does not state in the MOP to disregard oxygen and/or flow used only with feeds—AS it does in the Physiologic Definition. So we are inconsistent. I think we need to add to MOP, chapter 16 under oxygen and flow rat- to disregard the use of oxygen or flow rate if used only with feeds.
Please advise.....Nancy

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Coordinator SUPPORT Protocol
Date: Monday, May 22, 2006 3:30:31 PM

Rose
okay with me
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

-----Original Message-----
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Sent: Wednesday, May 17, 2006 10:30 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Cc: Zaterka-Baxter, Kristin; Neil Finer; Carolyn Petrie; Kathy J Auten; Wade Rich; Angelita Hensman
Subject: Coordinator SUPPORT Protocol

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Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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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: Monica Collins
To: Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.; Ellen Hale; Neil Finer; Ellen Hale
Subject: RE: SUPPORT
Date: Monday, May 22, 2006 11:35:44 AM

We'll get them out today!
Monica

From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
Sent: Mon 5/22/2006 9:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.; Monica Collins; Ellen Hale; Neil Finer; Ellen Hale
Subject: Re: SUPPORT

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> on Monday, May 22, 2006 at 10:33 AM -0500 wrote:
Wally and Monica

Can you send Ellen Hale/Barbara Stoll **TWO BLUE Oximeters?** If you are short, let me know.

Thanks
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, May 21, 2006 9:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins
Subject: Re: SUPPORT

Ok.
Wally

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

Sent: Sun May 21 08:28:31 2006
Subject: Re: SUPPORT

Ellen Hale will let me know first thing tomorrow morning.
I will let you know then.
Thanks for your help and dedication.
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins <MCollins@peds.uab.edu>
Sent: Sun May 21 09:06:59 2006
Subject: Re: SUPPORT

Rose: we can spare them. How many do you want us to send?
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Sun May 21 08:04:09 2006
Subject: Re: SUPPORT

I just heard back - they are ok for the next couple of days - we can have them go fed ex tomorrow.
Thanks
For getting back to me!
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Monica Collins <MCollins@peds.uab.edu>
Sent: Sun May 21 08:55:58 2006
Subject: Re: SUPPORT

Rose: I think Delta does it. I can call them. Let me know.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Sun May 21 06:45:22 2006
Subject: SUPPORT

Wally
Are you (or any of your staff aware of any same day delivery service between Birmingham and Atlanta?? Emory has 3 blue oxineters available as of last night along with consented twins + others. If the twins aren't randomized to blue it is not a problem. Let me know. Otherwise I may be in touch with you tomorrow am anyway to get Emory some blue oximeters (if you can spare them).

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

This is a good problem to have-- needing more oximaters than anticipated!!
Thanks to my terrific team
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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Monica Collins
Subject: Re: SUPPORT
Date: Sunday, May 21, 2006 9:54:43 AM

Ok.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Sun May 21 08:28:31 2006
Subject: Re: SUPPORT

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Rose

Sent from my BlackBerry Wireless Handheld

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Subject: SUPPORT

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Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT OXIMETERS
Date: Sunday, May 21, 2006 8:39:32 AM

Sorry, I had to mee(b) (6)
We are fine for the first of the week.
Thanks,
Ellen

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> on Saturday, May 20, 2006 at 6:32 PM wrote:

>Should I try to get them for you before monday am - it may be too late
>for fed ex saturday drop off - let me know.
>
>Thanks
>Rose
>---
>Sent from my BlackBerry Wireless Handheld
>
>
>----- Original Message -----
>From: Ellen Hale <ellen.hale@oz.ped.emory.edu>
>To: Higgins, Rosemary (NIH/NICHD) [E]
>Cc: Susie Buchter <susie.buchter@oz.ped.emory.edu>
>Sent: Sat May 20 18:07:12 2006
>Subject: Re: SUPPORT OXIMETERS
>
>
>Dear Rose,
> We have enrolled our 5th baby and 4 of the 5 are blue Masimo babies.
> We only have 3 blues left and if we have twins or more randomized to
>blue we will be short. We have plenty of orange but could use a few more
>blues.
>Thanks,
>Ellen
>
>

From: Nancy Peters
To: Kathy J Auten; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT pulse oximeters
Date: Friday, May 19, 2006 7:08:35 PM

Oximeter Serial Numbers are:

310846
310958
311004

310914
310945
310998

Let me know if you need any additional information.

Nancy

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Fri 5/19/2006 3:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Zaterka-Baxter, Kristin; Nancy Peters
Subject: RE: SUPPORT pulse oximeters

We will.

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 \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> wrote on 05/19/2006 02:35:12 PM:

> Kathy and Nancy -
> Let Kris know the oximeter serial numbers
> Thanks again
>
> Rose
>
>
> From: Kathy J Auten [mailto:auten002@mc.duke.edu]
> Sent: Friday, May 19, 2006 2:29 PM

> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: cotte010@mc.duke.edu; Ronald N Goldberg; Nancy Peters
> Subject: SUPPORT pulse oximeters
>
>
> Rose,
> Thanks for calling me back so quickly and for helping to arrange the
> loan of 6 pulse oximeters for our (b) (6) mothers.
> Although they are both quiet and may not deliver over the weekend,
> we will still need 3 blue and 3 orange oximeters when they do deliver.
> We will be borrowing them from Wake Forest. Nancy Peters and I have
> arranged to meet on the road between here and Winston-Salem tomorrow
> morning. If you lived closer, you could join us for breakfast at the
> Cracker Barrel in Elon!
> Have a good weekend.
> 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

From: Neil Finer
To: auten002@mc.duke.edu; Nancy Peters
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT pulse oximeters
Date: Friday, May 19, 2006 6:53:12 PM

Nice work Kathy and Nancy
Enjoy the breakfast.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 19, 2006 10:31 AM
To: Kathy J Auten
Cc: cotte010@mc.duke.edu; Ronald N Goldberg; Nancy Peters; Michael O`Shea; Neil Finer
Subject: RE: SUPPORT pulse oximeters

Thanks to all of you!!!
Rose

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Friday, May 19, 2006 2:29 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: cotte010@mc.duke.edu; Ronald N Goldberg; Nancy Peters
Subject: SUPPORT pulse oximeters

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Have a good weekend.
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

From: Ellen Hale
To: Higgins, Rosemary (NIH/NICHD) [E]; joa@rti.org; kzaterka@rti.org
Subject: SUPPORT
Date: Thursday, May 18, 2006 5:10:12 PM

We have reviewed our SUPP02 forms to see why we coded consents as not being requested. Here are the reasons for the 12 forms:

6 mom in active labor on admission

2 precip del. soon after admission

1 stat c/s

3 consent not in mom's language (have consents translated into Spanish now).

Except for the consent problem, all moms have been approached for consent as our IRB allows.

Hope this helps,
Ellen

From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Coordinator SUPPORT Protocol
Date: Thursday, May 18, 2006 4:52:51 PM

Yes- Michele

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD) [E]
To: alaptook@WIHRI.org ; Abhik Das ; ambal@uab.edu ; aaf2@po.cwru.edu ; Bradley.yoder@hsc.utah.edu ; Brenda Poindexter ; Carlo Waldemar (E-mail) ; Ed Bell ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Ivan Frantz ; Kennedy, Kathleen A ; Krisa VanMeurs (VanMeurs, Krisa) ; Kristi Watterberg ; kurt.schibler@cchmc.org ; cotte010@mc.duke.edu ; Michelle Walsh ; Mickey Caplan ; Oh William (E-mail) ; Pablo Sanchez ; papile@unm.edu ; Poole Kenneth (E-mail) ; Roger Faix ; Ronald GOldberg ; Seetha Shankaran ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; walid.salhab@utsouthwestern.edu
Cc: Zaterka-Baxter, Kristin ; Neil Finer ; Carolyn Petrie ; Kathy J Auten ; Wade Rich ; Angelita Hensman
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Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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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: Nancy Miller
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Pablo Sanchez; Walid Salhab
Subject: Re: Coordinator SUPPORT Protocol
Date: Thursday, May 18, 2006 2:39:58 PM

Rose,
Gay and I both vote yes for the submission.
Thanks,
Nancy

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05/17/06 9:29 AM >>>
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Thanks

Rose

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

From: Kurt Schibler
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Coordinator SUPPORT Protocol
Date: Thursday, May 18, 2006 11:11:29 AM

Hi Rose,
I vote YES to allow the coordinators to submit the Antenatal Consent study to the ACRP conference.
Thanks,
Kurt

On 5/17/06 10:29 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hi,
>
> The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007 They are asking that research proposals be submitted by June 30 for next year's meeting. **The submission would consist of the design of the protocol**.
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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

Bethesda, MD 20892

(For overnight delivery, use Rockville, MD 20852)

301-435-7909

301-496-3790 (FAX)

higginsr@mail.nih.gov

From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Coordinator SUPPORT Protocol
Date: Thursday, May 18, 2006 10:30:15 AM

Yes.
Richard

At 10:29 AM 5/17/2006, you wrote:

> Hi,
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> Rose
>
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> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
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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: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Breathing outcomes interviews
Date: Thursday, May 18, 2006 7:23:57 AM

Hi Rose,
after soon street fighting here at Duke we"ve decided that we will do the intake interviews and Rochester can do the rest of the interview. sorry for the confusion.
ron

"Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov>
To: "Ronald Goldberg" <goldb008@mc.duke.edu>
cc:
05/15/2006 11:39 AM
Subject: FW: Breathing outcomes interviews

Ron
Can you let me know if Duke or Rochester will do your SUPPORT pulmonary follow up telephone interviews?
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, May 04, 2006 4:42 PM
To: Ronald N Goldberg
Subject: FW: Breathing outcomes interviews

Ron,
I am working on some budget items and was told by Tim Stevens that Duke was not going to do their own interviews for the pulmonary outcomes study. Based on the response attached to the email from Ricki Goldstein in June, I was under the impression that your site was going to do the interviews. Tim them sent me the email below. I believe we had already awarded funds for your site to do the pulmonary follow up interviews in last year's budget. I do remember Ricki and Melody being quite adamant at the meeting in September that they wanted the Duke site to contact their own patients.

Let me know how you folks are going to proceed. Also, please let the staff

know to cc Carolyn or myself on the emails.

Thanks
Rose

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, May 04, 2006 4:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Breathing outcomes interviews

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Tuesday, November 29, 2005 11:32 AM
To: Stevens, Timothy
Cc: Ricki F Goldstein; newman@rti.org
Subject: Breathing outcomes interviews

Tim,
Dr. Goldstein, our FU PI, has just asked me to let you know that we would like Rochester to conduct the interviews for your study. We don't have the personnel to conduct them here. I hope this does not cause you any inconvenience.
Rick sends his regards.

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[attachment "Re Pulmonary outcomes secondary study.txt" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Coordinator SUPPORT Protocol
Date: Thursday, May 18, 2006 12:10:24 AM

AOK
Yes vote from 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:	Zaterka-Baxter, Kristin
To:	nfiner@ucsd.edu
Cc:	wrich@ucsd.edu; ellen_hale@oz.ped.emory.edu; Miller, Lucy C.; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	Coordinator Call tomorrow
Date:	Wednesday, May 17, 2006 5:53:11 PM
Attachments:	SUPP11[Rev 3-7-06] .doc 16.doc

Hi,
Just wanted to keep you up to date on a few issues that will be brought up tomorrow on the coordinators conference call re. Support:

1. If and infant has not reached 36 weeks, is on RA (no support/no 02) and has been taken off the masimo, does form Supp11 need to be completed for all time points. It currently is asking for data on 4 time points daily for mode of support, 02, flow rate (if nc) and alarm check until 36weeks or status. Should there be another way for infants who are off support to record that they are in RA daily only (form and MOP instructions attached).
2. Do we need a place to record the date the masimo is discontinued?
3. Form Supp05: a suggestion has been made to open the shaded sections of the form and record all information actually obtained at a given time rather than try to figure out which time slot is most appropriate to document date collected and a different time
4. Form Supp05a: a suggestion has been made to delete section "C" and for any reintubation/extubation with in 24hrs, complete a second form Supp05a.
5. ROP final exam missing data has been sent out to the sites with their center specific cases with final exam status pending. There may be question..
6. If an infant is in support and the family is deemed very unlikely to return for follow-up, how should this be handled?

That's it.
Thanks,
Kris

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	15 __ __/__ __/__ __ __ __ Month Day Year	16 __ __/__ __/__ __ __ __ Month Day Year	17 __ __/__ __/__ __ __ __ Month Day Year	18 __ __/__ __/__ __ __ __ Month Day Year	19 __ __/__ __/__ __ __ __ Month Day Year	20 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	21	22	23	24	25	26
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	27	28	29	30	31	32
	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year	__ __ / __ __ / __ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ___

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/____

Study Day	33 __/__/____ Month Day Year	34 __/__/____ Month Day Year	35 __/__/____ Month Day Year	36 __/__/____ Month Day Year	37 __/__/____ Month Day Year	38 __/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/____

Study Day	39 ___/___/____ Month Day Year	40 ___/___/____ Month Day Year	41 ___/___/____ Month Day Year	42 ___/___/____ Month Day Year	43 ___/___/____ Month Day Year	44 ___/___/____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/____

Study Day	45	46	47	48	49	50
	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year	__/__/____ Month Day Year
1. Scheduled Time: 06:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
2. Scheduled Time: 12:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
3. Scheduled Time: 18:00	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__
4. Scheduled Time: 23:59	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)	__:__ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.	__.__ Liters/Min.
(d) Oximeter Alarm Check	__:__	__:__	__:__	__:__	__:__	__:__

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	51 __ __/__ __/__ __ __ __ Month Day Year	52 __ __/__ __/__ __ __ __ Month Day Year	53 __ __/__ __/__ __ __ __ Month Day Year	54 __ __/__ __/__ __ __ __ Month Day Year	55 __ __/__ __/__ __ __ __ Month Day Year	56 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	57 __ __/__ __/__ __ __ __ Month Day Year	58 __ __/__ __/__ __ __ __ Month Day Year	59 __ __/__ __/__ __ __ __ Month Day Year	60 __ __/__ __/__ __ __ __ Month Day Year	61 __ __/__ __/__ __ __ __ Month Day Year	62 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: ____ Birth No: ___ Mother's Initials: ____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___/___/____

Study Day	63	64	65	66	67	68
	___/___/____ Month Day Year	___/___/____ Month Day Year	___/___/____ Month Day Year	___/___/____ Month Day Year	___/___/____ Month Day Year	___/___/____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	69 __ __/__ __/__ __ __ __ Month Day Year	70 __ __/__ __/__ __ __ __ Month Day Year	71 __ __/__ __/__ __ __ __ Month Day Year	72 __ __/__ __/__ __ __ __ Month Day Year	73 __ __/__ __/__ __ __ __ Month Day Year	74 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.
Date of 36 weeks ___ / ___ / __ __ __ __

Study Day	75	76	77	78	79	80
	__ __/__ __/__ __ __ __ Month Day Year	__ __/__ __/__ __ __ __ Month Day Year	__ __/__ __/__ __ __ __ Month Day Year	__ __/__ __/__ __ __ __ Month Day Year	__ __/__ __/__ __ __ __ Month Day Year	__ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___ / ___ / __ __ __ __

Study Day	81 __ __/__ __/__ __ __ __ Month Day Year	82 __ __/__ __/__ __ __ __ Month Day Year	83 __ __/__ __/__ __ __ __ Month Day Year	84 __ __/__ __/__ __ __ __ Month Day Year	85 __ __/__ __/__ __ __ __ Month Day Year	86 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)						
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

16.1.1 Instructions for completing the Respiratory Support Form after 14 Days (SUPP11)

This form is to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood, 7= No Support,
- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes).
  Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time-during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.
- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Coordinator SUPPORT Protocol
Date: Wednesday, May 17, 2006 2:41:23 PM

yes, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 17, 2006 10:30 AM
To: Abbot Laptook; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: Zaterka-Baxter, Kristin; Neil Finer; Carolyn Petrie; Kathy J Auten; Wade Rich; Angelita Hensman
Subject: Coordinator SUPPORT Protocol

Hi,
The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007. They are asking that research proposals be submitted by June 30 for next year's meeting. **The submission would consist of the design of the protocol**.

The link to the ACRP home page is <http://www.acrpnet.org/> for your reference.

Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.

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: Coordinator SUPPORT Protocol
Date: Wednesday, May 17, 2006 2:01:09 PM

YES – an excellent idea that should be encouraged.
Brenda

Hi,
The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007. They are asking that research proposals be submitted by June 30 for next year's meeting. **The submission would consist of the design of the protocol**.

The link to the ACRP home page is <http://www.acrpnet.org/> for your reference.

Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.

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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Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: William Oh
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jennifer Lefner; Abbot Laptook; adas@rti.org
Subject: RE: Lefner protocol
Date: Wednesday, May 17, 2006 12:22:11 PM

Rose: Thanks for the quick response. I am communicating with you from Vienna. It looks like Jennifer should write a protocol and submit to GDB committee. I think RTI involvement would make the protocol implementation more effective. We will include the RTI folks as co authors if that is the case. We should also figure out what the potential budget need would be for RTI analysis. Abhik can probably help us on this. I will cc this to him

Bill

William Oh, MD
Professor of Pediatrics
Brown Medical School
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101 Dudley St,
Providence RI 02905
office phone 401 274-1122 ext 1432
cell 401 714-(b) (6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wed 5/17/2006 12:10 PM
To: William Oh
Cc: Jennifer Lefner; Abbot Laptook
Subject: RE: Lefner protocol

It sounds like this would be considered a single site ancillary protocol using the Brown GDB data. The instructions in the NICHD NRN policies and procedures are as follows:

5.2.3 Ancillary Protocols

Ancillary protocols are those designed by a Center's PI, alternates, or other faculty members
in a Center in conjunction with the development of a primary protocol. Data for these protocols are normally from a single center. Ancillary protocols should not interfere with the hypotheses of the primary protocol and their implementation should not interfere with the progress of the primary protocol. They should be approved by the primary protocol subcommittee, which will recommend approval to the Steering Committee. Authorship of ancillary studies will be determined by the PI of the ancillary protocol and the PI of the Center.
Ancillary protocols are not supported by the NRN Data Center Data Center.
Ancillary studies involving more than one center generally require significant input from the Data Center in order to ensure efficiency and scientific integrity. Therefore, they ordinarily should be considered secondary protocols with establishment of a subcommittee or to an appropriate existing subcommittee. However, if the question proposed or the number of participating centers is so limited that Data Center data center involvement is not required,

ancillary studies may involve more than one Network center. As in single-site ancillary protocols, their implementation should not interfere with the progress of the primary protocol
and they must be approved by the primary protocol subcommittee and the Steering Committee. Authorship will [there is rarely a subcommittee for these nor is one usually needed] follow the principles outlined in the Authorship section. It may also include alternates
or other faculty members in the participating Center.

I would suggest submitting a brief protocol to GDB (outline attached) for approval. Are you planning on doing the analyses at Brown or RTI?

Thanks
Rose

From: William Oh [mailto:WOh@WIHRI.org]
Sent: Wednesday, May 17, 2006 12:02 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jennifer Lefner; Abbot Laptook
Subject: Lefner protocol

Rose:Jennifer Lefner is one of our Neonatology fellow who is my mentee and interested in clinical research dealing with nutrition. She is interested in looking at the effect of caffeine treatment in VLBW infants with apnea. Our pharmacy has electronically recorded caffeine intake of all infants in the NICU since April 2005. Jennifer has access to these data and would like to match the infants with Brown GDB data base to look at weight gain and other co-morbidities. I have run this by Abboy and he is ok with it.

I don't remember what the Network policy/process is for single center data access. Please advice.Please cc to Abbot and Jennifer

Thanks

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) (6)

From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Coordinator SUPPORT Protocol
Date: Wednesday, May 17, 2006 11:39:53 AM

Rose,

My vote is yes.
Thanks,
David

At 07:29 AM 5/17/2006, you wrote:

> Hi,
> The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007. They are asking that research proposals be submitted by June 30 for next year's meeting. The submission would consist of the design of the protocol.
>
> The link to the ACRP home page is <http://www.acrpnet.org/> for your reference.
>
> Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.
>
> 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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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Coordinator SUPPORT Protocol
Date: Wednesday, May 17, 2006 10:31:03 AM

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 17, 2006 10:30 AM
To: alaptook@WIHRI.org; Das, Abhik; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole, W. Kenneth; Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); walid.salhab@utsouthwestern.edu
Cc: Zaterka-Baxter, Kristin; Neil Finer; Petrie, Carolyn; Kathy J Auten; Wade Rich; Angelita Hensman
Subject: Coordinator SUPPORT Protocol

Hi,
The coordinators are requesting send in our Antenatal Consent study to the ACRP (Association for Clinical Research Professionals) Global Conference to be held in Seattle in April of 2007. They are asking that research proposals be submitted by June 30 for next year's meeting. **The submission would consist of the design of the protocol**.

The link to the ACRP home page is <http://www.acrpnet.org/> for your reference.

Please send me a yes/no vote by May 30 for submission of the protocol design for presentation at the April 2007 meeting.

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: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Cc: Neil Finer; Zaterka-Baxter, Kristin; Carolyn Petrie
Subject: RE: SUPPORT -note from Dr. Finer
Date: Monday, May 15, 2006 2:54:11 PM

Neil
We will continue to be supportive
From the cool lady
SS

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, May 15, 2006 1:56 PM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Cc: Neil Finer; Zaterka-Baxter, Kristin; Carolyn Petrie
Subject: SUPPORT -note from Dr. Finer

Hello Everyone
I wanted to keep you abreast of SUPPORT enrollments and other related issues.

We had a meeting in San Francisco regarding the Prospective Meta Analysis. Lisa Askie is heading this effort. The PIs of each trial were there – This includes the UK Edmund Hey, Australia, William Tarnow Mordi, Canada, Barbara Schmidt, and Cindy Cole PI for the US Post trial running, and SUPPORT. The discussions were broad, and as we move ahead there will be more details emerging about the kinds of data we wish to collect. The plan is that each study will publish its own results, as they are available, and that the collective data will start to accumulate and be published when all the studies have been completed. We did discuss the benefit of having the DSMCs of each trial in contact with each other – this will be further discussed, and would

serve to notify all trials of concerns related to any of the trials. As you know we shared our DSMC discussions with all of these trials. I did emphasize the difference between SUPPORT and all the other trials in that SUPPORT is a factorial design and has a ventilatory arm, which will be different from the other trials. In addition we would want to be cautious about combining respiratory information from other trials with the information from SUPPORT which represents protocolized randomized interventions

Current SUPPORT enrollments are now 273 as of the April report. Congratulations to Case Western for leading the restart of the trial with 11 enrollments, Houston with 4, Emory and Wayne State with 3 each, Brown with 2, and Dallas with 1. The new sites have not yet obtained IRB approval, and we will be planning site visits to assist them get started.

Please have a look at your screening logs and numbers as a review of these suggests that there is no uniformity in the actual screening with some large sites indicating that they have only screened a few patients (range from 3 to 94).

Please let Rose or I know if we can be of any assistance helping your site enroll infants.

I will continue top keep you informed of our progress, and we should have oximeter download data available for you as we obtain more patient data.

Be well
Neil

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT -note from Dr. Finer
Date: Monday, May 15, 2006 2:24:09 PM

Thanks Rose
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, May 15, 2006 10:56 AM
To: alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Cc: Neil Finer; Zaterka-Baxter, Kristin; Carolyn Petrie
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Be well
Neil

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higginsr@mail.nih.gov

From: Neil Finer
To: Kathy J Auten
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support
Date: Monday, May 08, 2006 3:16:01 PM

Great Kathy
Neil

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Monday, May 08, 2006 9:56 AM
To: Higgins, Rosemary (NIH/NICHD); Neil Finer; Wade Rich; Kris Zaterka-Baxter
Cc: Ronald N Goldberg; cotte010@mc.duke.edu
Subject: Support

Just wanted you to know that we enrolled our first SUPPORT subject today. The infant is concurrently enrolled in the Growth secondary. We will be approaching the mother for the MRI secondary in due course, and will let you know how that goes.
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

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; dale_phelps@urmc.rochester.edu; schaefer@rti.org
Subject: RE: ROP Eye Exams
Date: Thursday, May 04, 2006 1:29:44 PM

I agree
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, May 04, 2006 10:14 AM
To: dale_phelps@urmc.rochester.edu; schaefer@rti.org
Cc: Neil Finer
Subject: Re: ROP Eye Exams

These outcomes are quite appropriate.

Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Schaefer, Scott E. <schaefer@rti.org>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer <nfiner@ucsd.edu>
Sent: Thu May 04 13:01:08 2006
Subject: RE: ROP Eye Exams

OK, Here is the issue:

What adverse ROP outcome does SUPPORT want?

In Inositol, we are using surgery for ROP, or meeting criteria for surgery for ROP, or worse.

Using the last phrase (or worse). Stage 4a or stage 4b is worse than meeting criteria for surgery for ROP.

Therefore, I would say that we include stage 4a or stage 4b or stage 5 all as unfavorable outcomes for ROP status.

Dale Phelps

From: Schaefer, Scott E. [mailto:schaefer@rti.org]
Sent: Thursday, May 04, 2006 11:11 AM
To: Phelps, Dale
Cc: Schaefer, Scott E.
Subject: RE: ROP Eye Exams

Dr. Phelps,

I need your help to clarify the unfavorable outcomes for the retinal detachments. I only used the post-surgical values because of the 4b code that is listed in the MOP.

Retinal detachment stage 5: This includes "Post Surgical Retinal Detachment" Code 5 (Complete) and "Highest Stage in Any Zone" code 5 (Stage 5).

My question is with Retinal Detachment Stage 4b that is listed as an outcome. I previously listed "Post Surgical Retinal Detachment" Code 4 (stage 4b), but the "Highest Stage in Any Zone" Code 4 (Stage 4a or 4b) doesn't seem to fit the criterion. How should I proceed.

I can not compare to the dataforms because I am currently denied access to the SUPPORT dataforms and MOP. So I can't really fill in the table for you below.

Dale

Unfavorable:

Final Status as in MOP

Final Status in Tracking Program

type I threshold ROP

Threshold (New Type 1) question is Y (Yes)

Laser (or cryo or both) surgery for acute ROP

Surgery = 1 (Laser), 2 (Cryotherapy), or 3 (Both laser/cryo)

retinal detachment stage 5

Post-surgical Retinal Detachment = 5 (Complete)

[an infant can be retinal detachment stage 5 without having had surgery, this would also be unfavorable --dlp]

retinal detachment stage 4b

Post-surgical Retinal Detachment = 4 (Partial, does involve macula (stage 4b)

[your 2nd option is different from the first, it can occur either with or without surgery... I'm a little confused here. --dlp]

Worse than meeting criteria for Surgery, but without surgery:

stage 4a

stage 4b

stage 5

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, May 03, 2006 12:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Schaefer, Scott E.
Subject: RE: ROP Eye Exams

Hi Scott and Rose,

Here are my comments and suggestions. Please share with Neil when you think appropriate. Kris Zaterka-Baxter may also want to see them.

Dale

Dale L. Phelps, MD

Pediatrics and Ophthalmology

Pediatrics, Box 651

601 Elmwood Ave.

Rochester, NY 14642

585.275.2972

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 5/2/2006 7:14 PM
To: schaefer@rti.org; Phelps, Dale
Subject: Re: ROP Eye Exam

Scott
I will review this and get back to everyone on Thursday (I canjt view the attachments on the blackberry). At Dale's perceptive advice, we did remind everyone the importance of the ROP outcomes at the FU PI meeting yesterday.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: Schaefer, Scott E. <schaefer@rti.org>
To: dale_phelps@urmc.rochester.edu <dale_phelps@urmc.rochester.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Schaefer, Scott E. <schaefer@rti.org>
Sent: Tue May 02 14:44:46 2006
Subject: ROP Eye Exam

Attached is my preliminary analysis of the ROP Eye Exam Tracking. As you would think there is a lot of f

The Word doc contains an explanation of my assuptions and method. The Excel file contains a de-identified list of the cases and a summary table for the monthly report.

Scott E. Schaefer

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu
Subject: FW: NeOProM SF meeting agenda
Date: Wednesday, April 26, 2006 11:29:29 AM
Attachments: NeOProM protocol - draft V6 26Apr06.pdf
NeOProM meeting ASP 30Apr06 - agenda.doc

Wally and Rose
Here is some more information regarding the meeting for the Prospective Meta analysis to be held Sunday between 10:00 and 12:00 at the PAS. We meet at the registration desk at 10:00AM.
Neil

From: Lisa Askie [mailto:laskie@ctc.usyd.edu.au]
Sent: Wednesday, April 26, 2006 12:15 AM
To: ccole@bidmc.harvard.edu; bdarlow@chmeds.ac.nz; Neil Finer; Henry Halliday; colin.morley@rwh.org.au; schmidt@mcmaster.ca; williamt@westgate.wh.usyd.edu.au; win.tin@stees.nhs.uk; shey@easynet.co.uk
Subject: NeOProM SF meeting agenda

Dear NeOProM Collaborators,

Please find attached the proposed agenda for our meeting in San Francisco and a revised draft protocol with some of the suggested changes incorporated. Hopefully we can discuss many of the unresolved issues next Sunday morning. I also hope to send a tabulation of the current data coding for both BOOST 2 Aus/NZ and SUPPORT if I have time before leaving, so look out for that if reading your email again before the meeting.

Otherwise, see you in California soon.
Lisa

<><><><><><><><><><><><><><><><><><><><>
Lisa Askie PhD MPH

Research Fellow, School of Public Health
Manager, Australian Clinical Trials Registry

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<><><><><><><><><><><><><><><><><><><><>

Confidential: not for circulation or quoting

Appropriate levels of oxygen saturation for extremely preterm infants: a prospective individual patient data meta-analysis

The **Ne**onatal **O**xygenation **Pro**spective **M**eta-analysis (**NeOProM**) Collaboration

DRAFT PROTOCOL

CORRESPONDENCE TO:

Dr Lisa Askie
NHMRC Clinical Trials Centre
University of Sydney
Building F, 88 Mallett St
NSW 2050 Australia

Tel: ***+61 2 9562 5000***
Fax: ***+61 2 9565 1863***
Email: *laskie@ctc.usyd.edu.au*

NeOProM Collaboration is supported by:

- National Institutes of Health, USA
- Australian National Health and Medical Research Council
- Health Research Council of New Zealand
- UK Medical Research Council
- Canadian Institutes of Health Research
- NHMRC Clinical Trials Centre University of Sydney
- Cochrane Collaboration

Abstract

Background

Despite oxygen being one of the most commonly used therapies in the care of small or sick newborns, uncertainty regarding the most appropriate levels of oxygenation for extremely preterm infants has existed for over 50 years. It remains unknown whether the anticipated short term benefits (such as reduced respiratory and ophthalmic morbidity) of targeting oxygen saturation levels generally 'lower' from birth can be achieved without resulting in small, but important, increases in death and major disability rates for these vulnerable infants.

Methods/Design

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration has been formed to undertake a prospective individual patient data meta-analysis to answer this important clinical question. This approach is considered 'gold standard' of systematic review methodology. It provides the same strengths as a single large-scale randomised trial, but provides greater pragmatic flexibility, especially regarding the different regulatory and recognition needs that arise when multiple funding sources are required. This will be the first prospective meta-analysis undertaken in neonatology. Several randomised trials of similar design are now being planned and/or conducted worldwide. Together these trials plan to recruit approximately 6,500 infants which should provide sufficient sample size to detect a difference in death and/or major disability of as little as 4%.

Progress to date

A collaborative group was formed in 2003. The first participating trial will commence enrolment in 2005. Final results should be ready for presentation to, and discussion with, the NeOProM Advisory Group in 2012, with the main publication expected soon thereafter.

Background

Extreme prematurity (birth more than 12 weeks early at less than 28 weeks' gestation) affects approximately 1% of births.[1] These infants require costly care within a neonatal intensive care unit (NICU) and about 75% are discharged home alive.[2] Despite a life expectancy of 70 years, they sustain severe morbidity.[3] Their risk of chronic lung disease, poor growth, respiratory illness, hospital re-admissions, visual deficits, cerebral palsy, sensori-neural disability and cognitive, educational and behavioural impairment is higher than in term infants.[4] They account for most of the costs and disability from NICU care.[5] Their risk of visual deficit may be increasing.[6] Reducing these morbidities would enhance their quality of life and benefit their family and the community.[7]

Oxygen toxicity in very premature infants

Oxygen is the most common therapy used in the care of very premature infants. It has been associated with significant improvements in neonatal survival and disability.[8] However, these infants are highly sensitive to its harmful biochemical and physiological effects. While oxygen is essential for metabolism, its by-products - free radicals and reactive oxygen species - cause tissue injury. Toxic oxygen radicals are increased in hyperoxaemia (too much arterial oxygen)[9] and in re-oxygenation after hypoxaemia (too little arterial oxygen). Premature infants are vulnerable to oxidative stress because they lack antioxidant protection.[9] They lack plasma radical scavengers, such as Vitamin E or beta- carotene, antioxidant enzymes, such as glutathione peroxidase, and their red cells lack superoxide dismutase.

Hyperoxaemia can constrict or obliterate vessels in an immature eye and brain, causing ischaemic injury.[9] Less exposure to oxygen is a simple, logical strategy that could reduce oxidative stress and tissue injury and prevent morbidity in very premature infants. In healthy premature infants breathing air, arterial oxygen saturation is 85 - 98%, which is considered physiological. However, the optimum range of arterial oxygen to minimise organ damage, without causing hypoxic injury, is unknown.

How oxygen causes Retinopathy of Prematurity (ROP)

In early fetal life, the retina is avascular. Vessels grow out from the centre, controlled by vascular endothelial growth factor (VEGF), released by normal hypoxic retinal tissue. After premature birth, treatment with inspired oxygen may flood the retina with oxygen. When oxygen treatment stops, the ischaemic peripheral retina becomes severely hypoxic. There is abnormally high secretion of VEGF and new vessels and fibrous tissue proliferate and invade the vitreous. Fibrous contraction leads to retinal detachment and visual loss.[10] Destroying these proliferating vessels by ablative laser surgery can prevent retinal detachment. This saves central vision in some cases, but there is often residual visual loss. Of survivors <28 weeks' gestation, **50% have ROP, 12.5% have severe (Grade III/ IV) ROP,[2] 56% of these have surgery, but about 10% of those treated become blind**. New recommendations will result in more infants with severe ROP having laser surgery.[11] Of survivors of 28-29 weeks' gestation, <2% get severe ROP.[2]

Oxygen and lung disease

High inspired oxygen contributes to chronic lung disease (broncho-pulmonary dysplasia) which is associated with poor outcome.[12, 13] Improved survival has increased chronic lung disease, leading to poor growth, impaired neuro-development and greater health costs.

Oxygen and brain injury

As with any treatment, oxygen might increase disability by salvaging sick babies who would otherwise have died.[8] Oxygen may contribute to brain damage in premature infants, through oxidative stress and low cerebral blood flow. Oxidative damage to premyelinating oligodendrocytes in cerebral white matter is proposed as a mechanism of periventricular leukomalacia[14] - a form of white matter damage correlated with cerebral palsy. In premature infants, oxygen reduces cerebral blood flow velocity independently of the effects of hypocapnia or hypotension.[15]

These mechanisms may explain why hyperoxaemia was a risk factor for cerebral palsy in a study of 1105 preterm infants.[16] Hyperoxaemia in the first eight days was associated with twice the odds of cerebral palsy at 2 years, after adjusting for other variables. The adjusted odds of cerebral palsy increased eightfold for infants with the highest versus the lowest quintiles of exposure to hyperoxaemia, indicating a dose-response effect. Importantly, hyperoxaemia was defined as arterial oxygen above 60 mm Hg, in contrast with the long accepted upper limit of 80 mm Hg.[17, 18]

Previous trials of restricted or targeted oxygen in very premature infants

In a 2004 editorial in *Pediatrics*,[19] Dr William Silverman, formerly of Columbia University New York, states,

"...there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants. For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP-blindness, chronic lung disease and brain damage) was, and remains to this day, unknown."

The first case of ROP (originally called Retrolental Fibroplasia) was reported in 1942. By 1954, ROP had blinded about 10,000 infants.[19, 20] In 1954-56, 3 RCTs enrolling 341 infants proved that breathing unrestricted concentrations of inspired oxygen was a major cause of ROP.[21] Arterial oxygen levels were not measured, so the concentration of inspired oxygen could not be targeted to meet each baby's needs. To prevent ROP, all premature infants were restricted to breathing less than 40% inspired oxygen. In the next 20 years over 150,000 premature babies died of hypoxic respiratory failure.[8, 22-24] For every infant whose sight was saved, it is estimated that 16 died[8, 19, 22] and many others developed spastic diplegia.[23] The epidemic of blindness stopped – but at heavy cost. This might have been avoided had a larger RCT determined if oxygen restriction from birth increased or decreased death and disability.

The STOP ROP trial: The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity trial[25] used pulse oximetry to target lower (89-94%) or higher (96-99%) arterial oxygen saturation (SpO_2)[25] in 649 premature infants with early ROP. The higher range caused more adverse respiratory events, including pneumonia, chronic lung disease requiring oxygen and diuretic therapy.

The BOOST Trial: In the Benefits of Oxygen Saturation Targeting (BOOST) trial, reported in *New England Journal of Medicine,*[26] 358 infants born at less than 30 weeks' gestation were randomly assigned, *from ≥ 3 weeks after birth until they breathed air*, to target oxygen saturation (SpO_2) of 91-94% or 95-98%. This study aimed to decide if targeting higher SpO_2 improved growth and development. It showed that there was no evidence that higher SpO_2 improved growth or development, but did increase days of oxygen therapy and use of health care resources. Masked, adjusted oximeters were a

major innovation. Half were adjusted to display masked values 2% lower than actual SpO_2, the others displayed masked values 2% higher. Staff were unaware of actual SpO_2 and targeted a masked range of 93-96%. Masked oximetry was safe and acceptable to staff and parents. The authors concluded that RCTs are needed to determine how different SpO_2 levels *from the day of birth* affect ROP, chronic lung disease, growth, disability and mortality.[19, 26]

Current guidelines for levels of arterial oxygen to minimise the risk of ROP

A cohort study, reported in 1977, was unable to establish a relationship between arterial oxygen tension and retinopathy.[27] A range of 50–80 mm Hg became widely accepted,[17, 18, 28] but was based on professional consensus rather than evidence. A later study confirmed that ROP occurred more often with arterial oxygen tension above 80 mm Hg,[29] but did not determine if another limit was safer. Oximeters measuring functional SpO_2 display values about 1.5% higher than those measuring fractional SpO_2.[30] Normal fetal oxygen saturation is 70–80%.[31, 32] In transposing oxygen tensions of 50–80 mm Hg into equivalent arterial oxygen saturation, most clinicians have targeted functional SpO_2 90–95% (the mid range of what is considered physiological) with a minimum of 85%.[33]

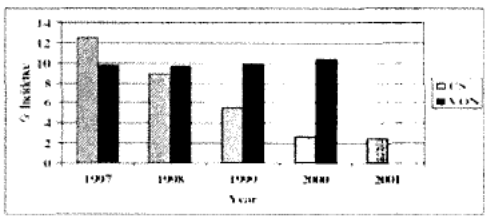
Four recent cohort studies of lower oxygen saturation targets in relation to short-term outcome

1. Tin showed that lower SpO_2 correlated with improved short term respiratory and growth outcomes in infants <28 weeks' gestation.[32] Alarm limits for SpO_2 in four NICUs ranged from 70–90% to 88–98%. Babies in the NICU targeting SpO_2 70-90% had less ROP surgery than those in the NICU targeting SpO_2 88-98% (6.2% *v* 27.2%: 80% relative risk reduction (RRR), $p < 0.01$). Survivors were ventilated less often (13.9 *v* 31.4 days), fewer needed oxygen at 36 weeks' postmenstrual age (18% *v* 46 % (61% RRR), and fewer were below the 3rd centile for weight at discharge (17% *v* 45%, 62% RRR) (all $p< 0.01$) while survival (52% *v* 53%) and cerebral palsy (15% *v* 17%) at one year were similar.[32]

2. Anderson reported less Grade III/ IV ROP (2.4% vs. 5.5%, $p<0.001$) and less ROP surgery (1.3% v. 3.3%, 61% RRR, $p<0.037$) in NICUs with functional SpO_2 upper limit ≤ 92% vs >92%.[34]

3. Sun studied 1544 infants weighing <1000 g in NICUs with upper limit SpO_2 of ≤95% vs >95%. NICUs with ≤95% limits had less Grade III ROP (10% vs 29%), surgery (4% vs 12 %, 67% RRR), chronic lung disease (27% vs 53%, 49% RRR) (all $P< 0.001$) and similar mortality (17% vs 24%).[35]

4. Chow[36] found that 83-90% functional SpO_2 was associated with less Grade III-IV ROP than 90 - 98% in historical controls. From 1998 to 2001, it fell from 12.5% to 2.5% (80% RRR, $p= 0.01$) and ROP surgery fell from 7.5% (6/80) to zero (0/188) (100% RRR, $p=0.0006$). Fewer infants had Grade III/ IV ROP than in the Vermont Oxford Quality Improvement Network (VON) (Figure to right).



These 4 studies strongly suggest that lower SpO_2 may reduce ROP surgery by 61-100%; chronic lung disease by 49 – 61%; and poor growth by 62%. Effects on mortality and sensori-neural outcome could be beneficial or harmful.

The unresolved question regarding appropriate levels of oxygen saturation

There are two opposing concerns. Less inspired oxygen (to target SpO_2 <90%) may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development.[37-39] More inspired oxygen (to target SpO_2 >90%) may increase severe ROP and chronic lung disease.[16, 32, 34-36] After recent studies,[32, 34-36] more NICUs are adopting lower SpO_2. This trend may increase before the risks and benefits are determined. The disastrous mistakes of the 1950s[17, 19, 20, 22, 24] show how rapidly opinions can shift, destroying the chance of obtaining reliable evidence.

Current developments: formation of the international NeOProM Collaboration

Worldwide demands to resolve the dilemma are intensifying. In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct the NeOProM (Neonatal Oxygenation Prospective Meta-analysis) Collaboration. The group has members in Australia, NZ, US, Canada, UK and elsewhere in Europe who interact frequently via email, teleconferences and at international meetings. Since July 2003, members have addressed over 20 national or international meetings. In December 2003, the NeOProM project was outlined in a commentary in *Pediatrics*.[40]

Several NeOProM Collaboration members have been successful in seeking support from their respective national funding agencies to conduct individual trials in their own countries, with a common core protocol and dataset, which will contribute to the prospective meta-analysis of all trials. Successful funding submissions have been awarded in Australia, Canada, New Zealand, USA and UK. One further planned trial in the USA will submit a funding application in 2007. See Appendix 1 for the listing of potential included trials.

Establishing the first Prospective Meta-Analysis (PMA) in neonatology: a major step forward

Each of these planned trials will recruit over a thousand babies, and will thus yield a great deal of useful information in their own right. However, none individually will be able to exclude the possibility that valuable short term benefits associated with giving babies less oxygen are not associated with a small but significant ***increase*** in death or serious neurosensory disability in survivors.

For example, the recently funded Australian BOOST-II trial which plans to recruit approximately 1,200 infants will be able to exclude a clinically important difference of 8% (from 37% to 45% or from 37% to 29%) in the major composite outcome of death or severe disability in survivors. This would mean one less infant would die or be disabled for every 12 given less oxygen. A smaller difference of 4% is also important as it would mean one less major outcome for every 20 infants given less oxygen. However, excluding a 4% difference requires approximately 6,500 infants, which no single country can recruit.

For this reason, the Principal Investigators planning these trials around the world have pledged their support for a prospective meta-analysis (PMA) of individual patient data from each of these studies. Combining the results from several trials of similar design using prospective meta-analysis methodology differs from a standard meta-analysis of trial results in several important ways.

Key features of prospective meta-analysis

A prospective meta-analysis (PMA) is a meta-analysis where studies (usually randomised controlled trials) are identified, evaluated, and determined to be eligible before the results of included studies are known or published. This methodology can help avoid some of the potential biases inherent in standard, retrospective meta-analyses. These can include publication bias (where studies with more positive results are more likely to be published and thus are more likely to be included in the analysis); selection bias of subjects and trials; and bias due to *post hoc* selection of study questions, eligibility criteria, outcome definitions or subgroups.[41]

The key features of PMA are to prospectively define and clearly specify the objectives, research question(s), specific aims, hypotheses, subject eligibility criteria, subgroups, predictors, outcomes (primary and secondary) and the analysis plans of eligible studies in advance of knowing or publishing individual trial results.[42] PMA provides more reliable estimates of treatment effects through prospectively planned combined analysis of large-scale randomized controlled trials. In addition to having greater power to detect meaningful modest differences in less frequent, clinically important outcomes, PMA provides adequate power to evaluate events in important subgroups underrepresented in smaller RCTs. Thus, PMA provides the same strengths as a single large-scale randomised study.

Another advantage is that PMA provides greater, pragmatic flexibility in achieving the objectives of a single mega-trial. Funding agencies often have different funding cycles, requirements, regulations and justifiable recognition needs. Through prospectively planned combined analysis of large, randomised trials, PMA accommodates funding agency variations, reduces costs to an individual funding agency for a mega-RCT, while providing the same strengths and benefits of a single mega-randomised study. In this regard, PMA sets an important precedent for future large neonatal trials. PMAs establish uniformity in common protocol among trials, data collection, outcomes, and rules whilst permitting flexibility in pre-specified protocol details and funding regulations. To protect the integrity of each individual trial, the main results are published in the group name and only after the principal results of each individual trial have been published. This method also has the flexibility to allow questions to be added after the PMA protocol has been developed provided the additional studies or questions are chosen in a manner masked to the results.

By establishing a collaboration between trialists of eligible studies, it is possible to collect individual patient data (IPD) and incorporate it into the meta-analysis. Using data collected from each individual within a trial, rather than relying on aggregate data from each trial, can improve the power and scope of the meta-analysis. In particular, a meta-analysis using IPD can enable more flexible and detailed sub-group analyses.[43, 44]

There are, however, some issues that require particular attention when using prospective meta-analysis methodology. These include ensuring the scientific integrity of both the individual trials and the PMA are maintained; reaching consensus on the goals of the PMA, what data to collect, how and when to collect them and how to maintain uniformly high quality data across all sites; defining the role of each of the Data Coordinating centres; defining if and how each of the trial's Data Monitoring Committees will interact and share findings; and establishing policies concerning analyses of the pooled data, publication of pooled analyses, and responsibility for the pooled database.

Previous experience with prospective meta-analysis

This will be the first-ever neonatal prospective meta-analysis. However, the methodology has been used extensively in other areas of health care, particularly in cardiovascular disease and cancer. Examples of this approach include two major prospective meta-analyses of cholesterol-lowering treatments (PPP and CTT).[41, 45] PPP was a prospectively planned combined analysis of three large-scale pravastatin trials over a minimum of 5 years. PPP contains data for over 19,500 patients and has the power to examine the effects of treatment on various mortality and cancer outcomes as well as the ability to evaluate important events in subgroups under-represented in previous trials.[46] The CTT Collaboration[41] is a prospective meta-analysis of 14 randomised trials of evaluating a fibrate or dietary modification on cholesterol levels. The CTT Collaboration has information on over 90,000 patients. These large PMAs provide more reliable estimate of the effects of cholesterol reduction on cause-specific mortality and of the effects on coronary mortality within important subgroups. The Blood Pressure Lowering Treatment Trialists Collaboration recently published[47] the results of a series of seven sets of prospectively-designed overviews that assessed the comparative effects of different blood-pressure lowering regimens on major cardiovascular results. These meta-analyses included data from 29 randomised trials and over 162,000 people and were able to establish conclusively the differential effects of different drug regimens on cause-specific cardiovascular outcomes.

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration will be coordinated by Dr Lisa Askie under the supervision of Professor John Simes in Sydney, Australia. Dr Askie was the lead author of BOOST trial publication[26] and has considerable experience in neonatal Cochrane reviews.[21, 48-50] She has recently spent two years at the UK Cochrane Centre in Oxford (with Professor Mike Clarke)[44] and the MRC in London (with Dr Lesley Stewart)[43] gaining expertise in individual patient data meta-analysis methods as a NHMRC Sidney Sax Postdoctoral Fellow. Professor Simes is the world's leading authority on prospective meta-analysis methodology.[41] The NeOProM protocol will be submitted to the Cochrane Collaboration Neonatal Review Group, and both the Cochrane Prospective Meta-Analysis Methods Group (co-convened by Prof Simes) and the Cochrane Individual Patient Data Methods Group (co-convened by Dr Lesley Stewart) will be notified and consulted for methodological advice as required. The Principal Investigators of each of the trials involved in NeOProM will be members of the Collaboration's Management Committee (see *Project Management*). Thus, this is an opportunity to adapt the methodologies of prospective meta-analysis and individual patient data meta-analysis, already well-established in other health care fields, for use in answering important neonatal questions.

Study design

Objectives

The primary objective of the NeOProM Collaboration is to meta-analyse data from several randomised trials to address scientific questions for which there may be inadequate power within individual studies.

The primary question to be addressed by this study is: Does less oxygen given to extremely preterm infants from birth or soon after, increase or decrease the composite outcome of death or major disability in survivors by 4% or more? NeOProM will have the statistical power to detect important risks or benefits in potentially conflicting secondary outcomes.

Hypotheses

Compared with functional oxygen saturation level (SpO_2) of 91-95%, targeting SpO_2 85-89% within 24 hours of birth, for a minimum of two weeks and thereafter until the infant reaches 36 weeks postmenstrual age (pma) or breathes air (whichever is achieved first), is associated with:

Primary hypothesis: <4% absolute risk difference from 42%[4,5] to 46% or from 42% to 38% (10% relative risk increase or 10% relative risk reduction (RRR)) in mortality and major disability at 2 years postmenstrual age (defined as gestational age plus chronological age).

Hypothesis 2: 2.4% absolute risk reduction (ARR) from 7%[2] to 4.6% (34% RRR) in ROP surgery.[11]

Hypothesis 3: (a) 10% ARR from 40%[2] to 30% (25% RRR) in risk of being treated with oxygen or on respiratory support at 36 weeks postmenstrual age; (b) fewer days being ventilated through an endotracheal tube; (c) fewer days of supplemental oxygen; (d) fewer infants discharged on home oxygen; (e) fewer deaths after more than 4 weeks of age attributed to pulmonary causes.

Hypothesis 4: (a) better weight gain between birth and 36 weeks postmenstrual age
(b) better head growth and weight gain between birth and 18-24 months postmenstrual age
(c) no increase in (i) treated patent ductus arteriosus or (ii) surgery for necrotizing enterocolitis

Sample size

A total sample size of 5230 (SUPPORT, BOOST II Aus, BOOST II NZ, BOOST II UK, COT) would have a 90% power to detect the differences in outcome in hypothesis 1, and power to detect even smaller differences that those outlined in hypotheses 2 and 3. With the addition of a further trial (US POST) the total sample size would increase to 6450. This would further increase the precision of the results by ensuring that a 4% increase in death or major disability could be detected (for example from 42% to 46%), with 95% confidence that the true result was an increase in this outcome from 42% to between 43.7% and 48.7% (RR1.10, 95% CI 1.04-1.16) - see Figures 1-3.

Figure 1: Sample NeoProM PMA result – increase in death or major disability of 4% (from 42% to 46%) in lower SpO2 target range group, for total sample size of 6450 infants

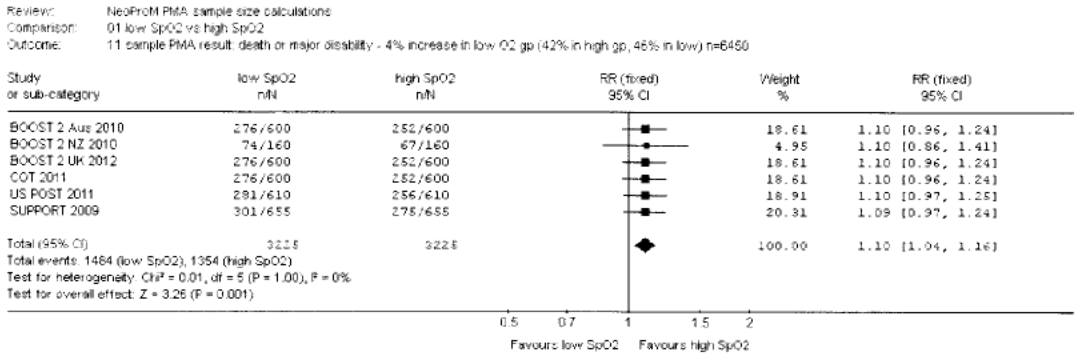


Figure 2: Sample NeoProM PMA result – decrease in ROP surgery of 2.4% (from 7% to 4.6%) in lower SpO2 target range group, for total sample size of 6450 infants

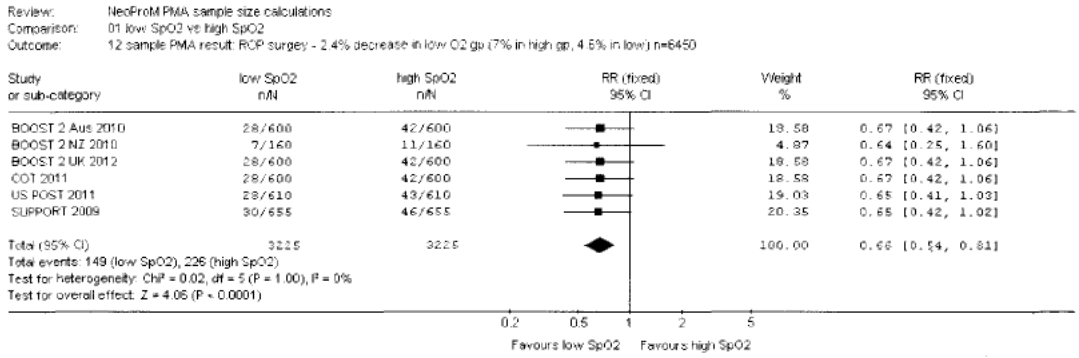
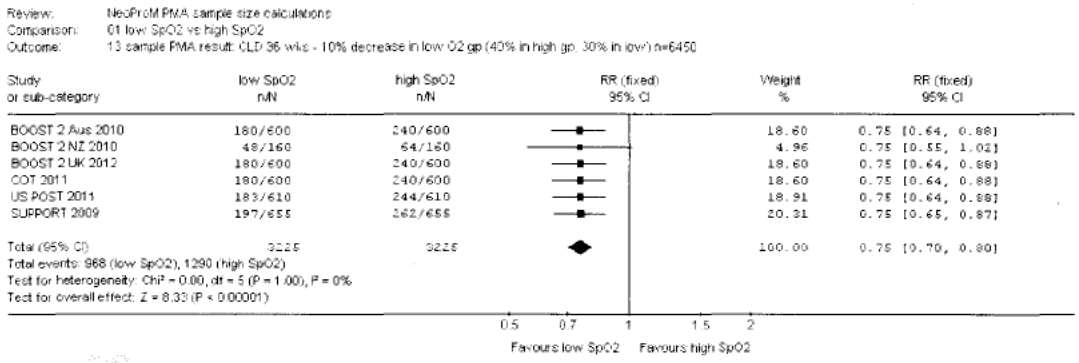


Figure 3: Sample NeoProM PMA result – decrease in CLD at 36 weeks of 10% (from 40% to 30%) in lower SpO2 target range group, for total sample size of 6450 infants



Identifying studies

The NeoProM Secretariat will be responsible for identifying potentially eligible studies. These are to be identified prospectively by a range of methods, including computer-aided literature searches of relevant bibliographic databases (such as MEDLINE and *The Cochrane Controlled Trials Register)*, manual searches of relevant journals, scrutiny of the reference lists of trials and review articles, scrutiny of abstracts and meeting proceedings, scrutiny of the relevant trial registers, and by inquiry among colleagues, collaborators and manufacturers of pulse oximeters. This will be undertaken at least twice per year. The Secretariat will be responsible for maintaining a register of eligible trials. Once a potentially eligible trial is identified, the investigators will be contacted, sent a copy of the NeoProM protocol and information describing the study will be sought. Newly identified studies will be included in the meta-analysis, provided they are registered before their results are known. Appendix 1 lists the currently registered eligible trials.

Eligibility criteria for studies to be included

The eligibility criteria for the types of study designs, participants, interventions, outcomes and other features of the studies to be included in the meta-analysis are listed below. Each potentially eligible study will be assessed independently by two members of the Secretariat, unblinded to the trial's identity. Any differences of opinion regarding the assessment of the eligibility criteria will be resolved by discussion between the two assessors. If differences cannot be resolved, a third member of the Secretariat will be asked to assess the study. If individual patient data are unavailable from an eligible trial, the trial will remain included in the meta-analysis and aggregate data used where possible.

a. Study design

Studies will be included if they are randomised trials. Quasi-random study designs, such as those using alternate allocation, will be excluded. The level of allocation concealment within each trial will be assessed according to the criteria outlined in the Cochrane Handbook,[42] and only those trials with adequate allocation concealment will be eligible. Once the individual patient data has been received from each trial, further assessments of the pattern of randomisation will be made via thorough data checking procedures. Participating trials will be required to register at inception on a publicly accessible trials registry.

b. Participants

Participants in the eligible trials will be infants born before 28 weeks' gestation and enrolled within 24 hours of birth.

c. Interventions

The interventions will be random assignment to either a lower (SpO_2 85-89%) or higher (SpO_2 91-95%) oxygen saturation target range, for an initial two week period, and thereafter until breathing room air or until at least 36 weeks postmenstrual age, whichever occurs first. Intervention assignment must be masked to parents, care-givers and outcome assessors by the use of pulse oximeters that have been adjusted to display either 3% above or below the infant's actual saturation value, within the 85-95% functional oxygen saturation range. Enrolled infants will be required to use the allocated trial oximeter for a minimum of two weeks, even if not requiring supplemental oxygen. Randomised trials with factorial designs that incorporate other intervention comparisons will be eligible.

d. Outcomes

Eligible trials must collect the core data items listed to follow. This list of core data items has been compiled following extensive consultation with the principal investigators of all known eligible trials, but is still under discussion and not finalised as yet. Eligible trials may choose to collect additional data items that will not be included in the PMA. More detailed definitions for the data items listed below can be found in Table 1. Details of the suggested coding for each of the following variables will be found in Appendix 2 (currently under development).

a. Characteristics of the trial

1 informed consent obtained
2 dates trial opened and closed to accrual
3 total number of infants randomised
4 treatments used in each arm of the trial
5 intended duration of treatments
6 definitions of key outcomes used in the trial
7 method of random allocation
8 stratification factors used
9 methods of allocation concealment

b. Characteristics of enrolled infants at trial entry

1 unique identifier for the enrolled infant, coded for anonymity
2 date and time of birth
3 gestational age at birth, or best estimate of expected date of delivery or date of mother's last menstrual period
4 date and time of randomisation
5 date and time intervention commenced
6 respiratory support immediately prior to intervention commencement
7 inborn or outborn status
8 antenatal corticosteroids
9 mode of delivery
10 weight at birth
11 gender
12 singleton or multiple birth
13 5 minute Apgar score

c. Infant data at 36 and 40 weeks postmenstrual age

1 weight
2 FiO_2 or rate of nasal flow oxygen
3 other measures of respiratory support

d. Infant data at discharge from hospital

1 total days with endotracheal or tacheostomy tube
2 total days of CPAP
3 date and gestational age when last received supplemental oxygen
4 date and gestational age when trial intervention ceased
5 surfactant treatment
6 PDA requiring treatment
7 NEC
8 postnatal steroids for lung disease
9 major cerebral abnormalities on cranial ultrasound
10 ROP outcomes: maximum grade, treatment with oxygen or surgery
11 care in non-tertiary unit prior to discharge
12 date and gestational age at discharge home
13 discharge home on supplemental oxygen
14 death before hospital discharge

e. Child data at 18-24 months corrected age

1 death between hospital discharge and 18-24 months corrected age
2 Bayley developmental assessment scores
3 visual outcomes
4 hearing outcomes
5 cerebral palsy
6 growth measures
7 re-admissions to hospital up to 18-24 months corrected age

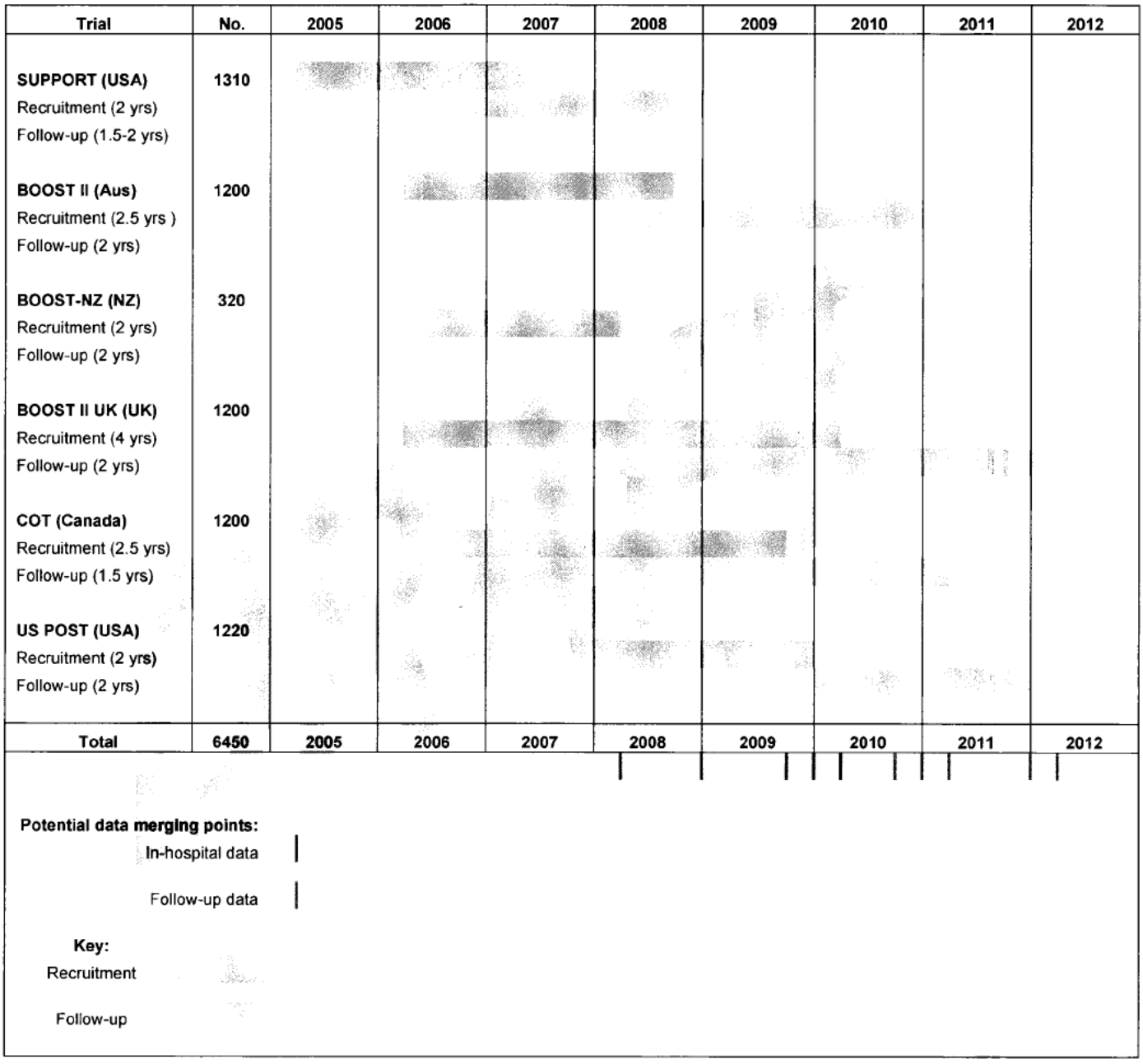
Data collection, data management and confidentiality

The individual patient data provided by the NeOProM Collaborators will be de-identified, re-coded as required and stored in a custom-designed database. It will not include any patient identifying information such as names or addresses. Data will be stored at the NeOProM Data Coordinating Centre. Electronic data will be located on a secure, password protected network server. Copies of any hardcopy data will be stored in locked filing cabinets until converted into electronic format, and will then be securely destroyed. Only authorised personnel will have access to the data. All data will be securely stored and archived according to the policies of the major funder(s).

The data provided for infants in each trial will be checked with respect to range, internal consistency, consistency with published reports and missing items. Trial details such as randomisation methods, and timing of the interventions will be cross-checked against any published reports, trial protocols and data collection sheets. Integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of prognostic factors across treatment groups (taking into account stratification factors). Inconsistencies or missing data will be discussed with the individual trialists and attempts will be made to resolve any problems by consensus. Each trial will be analysed individually, and the resulting analyses and trial data will be sent to the trialists for verification.

Data will be sought from each trial at prospectively specified intervals as outlined below. The date by which hospital-based outcomes and longer-term followup results will emerge from the studies will guide the timetable for seeking data from individual trialists. Trial data submitted to the NeOProM Secretariat will be held in strict confidence and will not be used in any publication without the permission of the responsible trialists. Particular care will be taken to ensure that the data collection and analysis procedures do not compromise any of the individual trials.

Proposed timetable for NeOProM data collection and receipt



Data monitoring procedures

Prospectively collected, de-identified (groups randomly labelled A and B, rather than lower or higher SpO_2), accumulating summary data will be made available to the individual Data Monitoring Committees of participating trials at pre-specified timepoints that have yet to be decided. The data items to be made available to individual trial Data Monitoring Committees will also be pre-specified, but are yet to be decided. The NeOProM Advisory Group will consult and decide on these procedures prior to the first potential data merging timepoint (see proposed timeline page 14). The chairpersons of each of the ongoing individual trial Data Monitoring Committees will meet (via teleconference) following each data receipt timepoint for discussion of the de-identified, accumulating summary data.

Because different oxygen targets may have competing risks, it is essential that sufficiently large numbers of recruits are allowed to accumulate to be able to demonstrate net clinical benefit or harm. That is, evidence of net clinical benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment to the prospective meta-analysis because of a 3% reduction in severe ROP in the lower oxygen group, before the project had accumulated sufficient power to exclude a 4% increase in mortality or severe neuro-developmental impairment in the same group.[51-55] Recommended stopping rules for the overall meta-analysis will be developed by the NeOProM Steering Group for consideration by individual trial Data Monitoring Committees.

Planned analyses

This section contains a summary of the planned analyses. The full, detailed analysis plan will be discussed and agreed upon by the NeOProM Collaborators before any data have been analysed. The detailed analysis plan will be made available in a separate document.

Analysis will be of all infants ever randomised and will be based on intention-to-treat. In the main analyses a two stage approach will be taken. Outcomes will be analysed in their original trial and then these separate results will be combined to give an overall measure of effect. A fixed effect model will be used and the assumption of homogeneity of treatment effects will be tested using the chi squared test. The I^2 statistic will also be used to assess consistency of results.

1. Outcomes to be analysed

The main analyses comparing targeting a lower oxygen saturation range (SpO_2 85-89%) with a higher one (SpO_2 91-95%) will be undertaken for all outcomes listed below.

a. Primary outcome

- composite outcome of death or major disability by 18-24 months postmenstrual age (gestational age plus chronological age). Major disability is any of the following: Bayley III Developmental Assessment MDI score <70 (-2SD), severe visual loss (cannot fixate or is legally blind (<3/60 vision, 1.3 logMAR in both eyes), cerebral palsy with inability to walk at 18-24 months postmenstrual age, or deafness requiring hearing aids.

b. Secondary outcomes

- retinal surgery (performed if Type I ROP or threshold ROP occurs[10])
- duration of oxygen therapy, defined as (a) oxygen at 36 weeks postmenstrual age, (b) days of endotracheal intubation (c) days of CPAP, (d) days of oxygen, (e) days on home oxygen
- oxygen requirement at 40 weeks postmenstrual age
- patent ductus arteriosus diagnosed by ultrasound and requiring medical or surgical treatment
- necrotising enterocolitis requiring surgery
- weight at birth, 36 weeks, discharge home and 18-24 months corrected age
- retinal structure at one year or when last seen
- re-admissions to hospital up to 18-24 months postmenstrual age
- cerebral palsy and unable to walk at 18-24 months postmenstrual age
- blindness (<3/60 vision, 1.3 logMAR in both eyes)
- deafness requiring hearing aides
- mean Bayley III MDI and PDI scores
- death after 4 weeks chronological age attributable primarily to pulmonary causes

2. Planned sub-group analyses

The effect of the intervention (higher or lower oxygen saturation targeting) may be differential due to certain characteristics of either the infant or the way the intervention was delivered (for example, timing of commencement or cessation). These possible effects will be explored by the following sub-group analyses.

a. Patient-level characteristics

- gestational age (<26 weeks / ≥26 weeks)
- surfactant treatment
- inborn or outborn status
- SpO_2 lability

b. Intervention-level characteristics

- time of intervention commencement (≤6 hours / >6 hours)
- time of intervention cessation (until breathing room air or at 36 weeks postmenstrual age whichever occurs sooner / until breathing room air or at discharge home whichever occurs sooner / until breathing room air irrespective of intervention cessation date - including infants receiving the intervention at home)

3. Planned sensitivity analyses

To assess whether results are robust to different methods of analysis and trial quality the following sensitivity analyses will be conducted:

- comparison of analyses using random effects and fixed effect models
- weighted analyses of outcomes for different degrees of oxygen saturation separation[45]

4. Additional analyses

Depending on what data are available, the level of heterogeneity encountered and available time a one-stage modeling approach may also be undertaken to further explore important key outcomes as appropriate.

Ethical considerations

Parents of participants in the individual trials have previously assented to participation by their children in their respective trial. The data for this project are to be used for the purpose for which they were originally collected and are available through an agreement between all trialists of the NeOProM Collaboration. These trialists remain the custodians of their original individual trial data at all times and have the right to withdraw some or all of their data from the analyses. Data are provided on the stipulation that all trials have received ethical clearances from their relevant bodies.

Project management

Membership of the NeOProM Collaboration will include representative(s) from each of the trials contributing data to the project with an accompanying project coordination and data management structure as described in this section. The membership and responsibilities of each of these management groups is as follows:

a. Steering Group

The Secretariat will be responsible for day-to-day project management decisions and will meet approximately 4-6 times per year, usually via teleconference. Membership: L Askie[1] (chair, project co-ordinator), C Cole[2], B Darlow[3], N Finer[4], E Hey[5], B Schmidt[6], J Simes[1], W Tarnow-Mordi,[7] and the Principal Investigator of any other included trials.

[1] NHMRC Clinical Trials Centre, University of Sydney, Australia;
[2] Beth Israel Deaconess Medical Center, Boston, USA;
[3] Christchurch School of Medicine, New Zealand;
[4] Division of Neonatology, University of California San Diego Medical Center, USA;
[5] Yorkshire, UK;
[6] Department of Pediatrics, McMaster University, Canada;
[7] Neonatal Intensive Care Unit, Westmead Hospital, Sydney, Australia.

b. Advisory Group

In addition to members of the Steering Group, all principal investigators of eligible trials will be contacted and invited to become members of the NeOProM Advisory Group. The aim of the Advisory Group is to facilitate representative input from the participating trialists. Members of the Steering Group will also be able to co-opt other international experts to the membership of the Advisory Group as required. The Advisory Group will communicate regularly via email, and will meet approximately twice per year either in person or by teleconference. Membership (in addition to the above-named members of the Steering Group) includes: E Asztalos, K Barrington, P Brocklehurst, W Carlo, P Davis, L Doyle, D Ghersi, H Halliday, W Hay, D Henderson-Smart, R Higgins, A Lindblad, C Morley, N Paneth, D Phelps, Ro Roberts, J Sinclair, R Soll, A Solimano, L Stewart, W Tin, R Whyte, and other members as deemed appropriate by the NeOProM Steering Group.

c. Project coordination and data management centre

The project will be coordinated from the NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia. The coordination and data management centre will be responsible for the daily management of the project including correspondence, newsletter production, maintaining current trialist contact information, meeting / teleconference organisation, as well as the receipt, storage, and analysis of project data as directed by the Steering and Advisory Groups.

d. Collaborators' meetings

All members of the NeOProM Steering and Advisory Groups will be invited to attend regular Collaborators' meetings. These meetings will be scheduled, where possible, to coincide with the annual Society for Pediatric Research conferences in the USA. The meetings will be designed to allow maximum input from the participating trialists into the design, conduct, analysis and reporting of the project's results.

At key stages of the data collection and analysis process, 'free-standing' Collaborators' meetings will be held. At these meetings the project results, data analysis issues and publication plans will be presented for discussion. Previous experience with other individual patient data and prospective meta-analysis projects have indicated that such meetings are very important for effective communication, timely data collection and meaningful interpretation and dissemination of results in these large, collaborative projects. The dates for Collaborators' meetings will be set by the Secretariat, in consultation with the Advisory Group.

Funding

Funding for the NeOProM Collaboration will be sought from national medical research agencies known to be supportive of large, collaborative, multinational projects and which have experience in funding this type of research methodology. This may include the National Health and Medical Research Council (NHMRC) of Australia, the UK Medical Research Council, the National Institutes of Health (USA) and others. Additional support will be provided by the various institutions to which members of the Secretariat and Advisory Groups belong. This project is being conducted independently of any commercial organisations.

Publication policy

Each of the participating trials will be able to publish their individual results prior to publication of the final PMA results. Each of the participating trials will include reference to the NeOProM Collaboration in the published abstract and, if possible, in the text of their main individual trial publication. Suggested text for inclusion in individual trial abstract publications would be: "More reliable conclusions will be possible when these results are pooled with those of similar trials in the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration."

Once finalised, the NeOProM protocol will be published in either a print or electronic journal prior to undertaken any analyses. A detailed analysis plan will be finalised and made publicly available prior to commencing the analyses.

To be eligible for inclusion in the first cycle publication of the main NeOProM results, participating trials will need to have commenced recruitment prior to a date to be set by the NeOProM Steering Group. Once the results of each of the participating trials are available in the public domain, the results of the combined PMA will be presented to, and discussed with, members of the NeOProM Collaboration. The main manuscript will be prepared by the Steering Group, and then circulated to the Advisory Group for comment and revision. The revised draft paper then will be re-circulated to all members of these Groups for comment before publication. All publications using these combined data will be authored in the name of the NeOProM, as follows: the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration, with the names of the collaborating trialists listed separately elsewhere in the manuscript.

Summary

Despite oxygen being one of the most commonly used therapies in the care of immature or sick newborns, uncertainty regarding the most appropriate levels of oxygenation for extremely preterm infants has existed for over 50 years. It remains unknown whether the anticipated short term benefits (such as reduced respiratory and ophthalmic morbidity) of targeting oxygen saturation levels generally 'lower' from birth can be achieved without resulting in small, but important, increases in death and disability rates for these vulnerable infants.

The NeOProM Collaboration has been formed to undertake a prospective individual patient data meta-analysis to address this important clinical question. This approach is considered the 'gold standard' of systematic review methodology. It provides the same strengths as a single large-scale randomised trial, but provides greater pragmatic flexibility, especially regarding the different regulatory and recognition needs that arise when multiple funding sources are required. This will be the first prospective meta-analysis undertaken in neonatology. Several randomised trials of similar design are now being planned and/or conducted worldwide. Together, these trials plan to recruit approximately 6,500 infants, which is a sufficient sample size to detect a difference in death and/or major disability of as little as 4%. The first participating trial commenced enrolment in 2005. Results should be ready for publication by 2012.

Appendix 1

List of potential eligible trials and their characteristics

Appendix 2

Suggested coding for core dataset variables (under development, not yet finalised)

Competing interests

None declared.

Acknowledgements

In addition to the named members of the NeOProM management groups, the following people have contributed to the success of the Collaboration: William Silverman, Iain Chalmers. The NeOProM Collaboration is dedicated to the memory of Bill Silverman who ..... *[write some nice words here]* .

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Table 1

Key definitions for enrolment characteristics and outcomes measures

Enrolment characteristics	Definition
inborn / outborn status	infant born at a hospital with neonatal intensive care facilities (inborn) or at a hospital without neonatal intensive care facilities (outborn)
age at intervention commencement	age (in minutes, hours) after birth when the study oximeter was placed on the infant and thus the targeting of the allocated saturation target range was commenced
Primary outcome components	**Definition**
mortality	death before 18-24 months corrected age follow-up; cause of death categories
neuro-developmental delay	Bayley Developmental Assessment MDI score <70 (-2SD),
severe visual loss	cannot fixate or is legally blind (<6/60) in both eyes
cerebral palsy	inability to walk at 18-24 months postmenstrual age
deafness	requiring hearing aids in either ear
Secondary outcomes	**Definition**
retinal surgery	laser or cryotherapy used for ROP treatment
maximal ROP stage before discharge	using International Classification of Retinopathy of Prematurity definitions
ROP treatment with oxygen therapy	prescription of high range oxygen saturation targeting for a short period to arrest the progression of pre-threshold ROP
duration of oxygen therapy	postmenstrual age when supplemental oxygen no longer required
patent ductus arteriosus	diagnosed by ultrasound and requiring medical or surgical treatment
necrotising enterocolitis	radiological diagnosis, clinical history plus either pneumatosis intestinalis, or portal vein gas, or a persistent dilated loop on serial X-rays
age at intervention cessation	postmenstrual age when targeting the allocated oxygen saturation range ceases
major cerebral abnormality	ventriculomegaly, intraparenchymal echodense lesion, porencephalic cysts, cystic periventricular leukomalacia, cortical atrophy no resolved post-discharge

Appendix 1

List of registered eligible trials as at October 2005

1. Eligible trials: funded

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication
SUPPORT	USA	1,310	April 2005	June 2007	Dec 2008	June 2009
BOOST-II	Australia	1,200	Mar 2006	Sept 2008	Dec 2010	Apr 2011
BOOST-NZ	NZ	320	Mar 2006	Mar 2008	June 2010	Sept 2010
BOOST-II UK	UK	1,200	April 2006	April 2010	April 2012	Dec 2012
COT	Canada	1,200	Aug 2006	Aug 2009	Feb 2011	June 2011

2. Eligible trials: funding applications submitted

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication

Nil further at this time.

3. Eligible trials: funding applications in preparation

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication
US POST	USA	1,220	to be determined: plans for funding re-submission underway			

Appendix 2

Suggest coding for core dataset variables

under development, not yet finalised

Detailed coding of the core NeOProM dataset will be finalised in consultation with full NeOProM Advisory Group once established.

However, common key endpoints have been agreed, in principle, across all participating trials - see draft NeOProM protocol.

Variable coding for BOOST II Aus / BOOST NZ available from NeOProM Secretariat.

NeOProM Neonatal Oxygenation Prospective Meta-analysis Collaboration

COLLABORATORS' MEETING

Date: Sunday 30th May 2006
Time: 10am-12pm
Venue: APS / SPR meeting, San Francisco, USA
[meet at registration desk, straight after late breaker session]

Attendees:
Lisa Askie (chair)
Brian Darlow (NZ)
Neil Finer (USA)
Henry Halliday (UK)
Colin Morley (Australia)
Barbara Schmidt (Canada)
William Tarnow-Mordi (Australia)
Win Tin (UK)
others??

Apologies:
Cynthia Cole?
Edmund Hey

AGENDA

1. Welcome
   1.1. official name, membership, proposed management structure
   1.2. overall aims and objectives

2. Protocol review
   2.1. Data Safety Monitoring Committee interactions
   2.2. publication policy
   2.3. core dataset: which items, definitions, data coding
   2.4. oxygen saturation data: storage and management, analysis plans

3. Future plans
   3.1. proposed timeline
   3.2. ongoing management
   3.3. funding plans

4. Next meeting
   4.1. date
   4.2. format

NeOProM Coordination Centre:
NHMRC Clinical Trials Centre
University of Sydney
Bld F, 88 Mallett St, Camperdown
NSW. 2050. Australia
Tel + 61 (0)2 9562 5000
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email: neoprom@ctc.usyd.edu.au

NeOProM Collaboration is supported by:

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wade Rich; Nancy.Miller@UTSouthwestern.edu
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Deviation?
Date: Monday, April 24, 2006 9:58:04 PM

Hello Everyone.
I was traveling today and just got in to my hotel. The presence of a clinically significant PDA is an adequate reason to not extubate and thus the decision to not extubate this infant is in keeping with the SUPPORT Protocol, and is not a violation.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 4/24/2006 12:16 PM
To: Das, Abhik; Neil Finer; Wade Rich
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Deviation?

The protocol states under extubation criteria for control infants:

* Absence of clinically significant PDA (Defined as bounding pulses, audible

murmur and Echo confirmation of L-R shunting with increased LA/Ao size

Thus, I would not call this a protocol violation or deviation.

Rose

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, April 24, 2006 3:11 PM
To: Neil Finer; wrich@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin
Subject: FW: SUPPORT Deviation?

What do you guys think? My feeling is that since intubation is allowed

for PDA, this is not really a protocol violation.

Thanks

Abhik

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

From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]

Sent: Monday, April 24, 2006 3:06 PM

To: Das, Abhik

Subject: Re: SUPPORT Deviation?

Abhik,

I'm wondering if I need to fill out a protocol deviation. We have a baby randomized to the control arm of SUPPORT who met all of the criteria to be extubated. He wasn't extubated because he had a symptomatic PDA and was going to be treated with indocin. I know the protocol allows for the baby to be intubated due to a PDA but I don't think there is a form to explain that is why this extubation wasn't done. Do I need to fill out a protocol deviation to explain the situation?

Thanks,

Nancy

Nancy A. Miller, R.N.

Department of Pediatrics

Division of Neonatal-Perinatal Medicine

UT Southwestern Medical Center at Dallas

5323 Harry Hines Blvd. E3-502

Dallas, Texas 75390-9063

214-648-3780

pager 972-206(b) (6)

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; Neil Finer
Cc: "Zaterka-Baxter, Kristin"
Subject: RE: SUPPORT Deviation?
Date: Monday, April 24, 2006 3:21:06 PM

I just sent the same answer. Frightening but true.
wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 24, 2006 12:16 PM
To: Das, Abhik; Neil Finer; wrich@ucsd.edu
Cc: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Deviation?

The protocol states under extubation criteria for control infants:
· Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

Thus, I would not call this a protocol violation or deviation.

Rose

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Thanks

Abhik

-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Monday, April 24, 2006 3:06 PM
To: Das, Abhik
Subject: Re: SUPPORT Deviation?

Abhik,
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Thanks,
Nancy

Nancy A. Miller, R.N.
Department of Pediatrics
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5323 Harry Hines Blvd. E3-502
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214-648-3780
pager 972-206-(b) [redacted]

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan
Cc: Neil Finer
Subject: RE: Slide; SUPPORT
Date: Friday, April 21, 2006 5:46:03 PM

Hi Ivan,

I think that rose has done an excellent job in explaining these issues. The major tension that currently exists is whether early CPAP, as practiced by Columbia, is associated with better outcomes than other approaches. The major problem with the Columbia data is that only 50% of the infants at Columbia that required intubation actually received surfactant. Your center is currently practicing the approach with the best evidence, as were many of the units in the network prior to the trial. There had been a drift toward the use of CPAP in some infants in many centers whereas some centers had already converted to early CPAP. The potential advantages of CPAP are the availability to avoid intubation and ventilation, and the potentially lower rate of chronic lung disease, especially if intubation is avoided. There are some more recent studies that would suggest the changing from early surfactant to CPAP, while not associated with dramatically improved outcomes, did tend to show lesser exposure to oxygen - Jegatheesan, P.; Keller, R. L., and Hawgood, S. Early variable-flow nasal continuous positive airway pressure in infants < or =1000 grams at birth. J Perinatol. 2006 Mar; 26(3):189-96. There are other studies such as that of Sandri and Thompson, which have compared CPAP to other initial approaches, albeit in more mature infants and have not shown any substantial outcome difference. All of these references I believe were in the presentation I made at the Network Steering Committee and I would be happy to talk with you if you think it would help. I tend to sell the support trial on the basis of the following:

1. There has been a substantial increase in the use of early CPAP. In many centers, as a replacement for early surfactant without the evidence to demonstrate that this approach is superior to early surfactant.
2. The outcomes from Columbia are difficult to evaluate because of their very infrequent use of early surfactant as they tended to treat children at 12 hours of age or later, well outside of any early surfactant windows - Ammari, A.; Suri, M.; Milisavljevic, V.; Sahni, R.; Bateman, D.; Sanocka, U.; RuzalShapiro, C.; Wung, J. T., and Polin, R. A. (Polin RA/Columbia Univ Coll Phys & Surg/Dept Pediat/Div Neonatal Perinatal Med/3959 Broadway BHS 115/New York,NY 10032 USA). Variables associated with the early failure of nasal CPAP in very low birth weight infants. Journal of Pediatrics. 2005; 147(3):341-347; ISSN: 0022-3476.
Notes: English Article
3. The support trial is designed to compare early CPAP with early surfactant either prophylactic or early, and is powered to look at important long-term outcomes.

Without this and the other trials, COIN and VON, neither of which are looking at infants of 24 weeks, VON only evaluates infants of 26 weeks or greater, we will not be able to definitively determine whether CPAP applied in the delivery room is substantially equivalent to surfactant. One final point, we have indicated in the protocol that CPAP infants who require intubation should receive surfactant if intubated in the first 48-72 hours. I hope this information is helpful. Please let me know if you would like anything further from me.

Regards,
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, April 21, 2006 12:14 PM
To: Frantz, Ivan
Cc: Neil Finer
Subject: RE: Slide; SUPPORT

Hi Ivan,

Attached is a graph from the publications subcommittee which is extremely positive for the NRN.

I have copied Neil Finer for assistance with your second question as he may have more information as we did repeatedly discuss what was done across the network sites.

With respect to SUPPORT, we had many centers who used early surfactant prior to initiation of the trial. In fact, one site, Cincinnati, had one hospital that used "prophylactic" surfactant and another which used early CPAP - so they had both directions to deal with for the equipoise issue. I believe that Alabama and Yale were also using early CPAP at the start of the trial.

One bit of information that may help to generate equipoise - All of the surfactant trials which showed improvement in infants were done is an era of low antenatal steroid use (mid 1980's to early 1990's). It was not until 1995 (NIH Consensus statement) that the rate of antenatal corticosteroid use really rose to the 80-90% levels of today. Thus, the infants may be slightly more mature from a pulmonary standpoint due to the benefits of antenatal steroids than the infants in the surfactant trial era. So if there endogenous surfactant systems are a little more mature, CPAP may offer positive pressure to maintain FRC and intubation may be avoided. This helped at some centers to generate equipoise for the study.

If folks are concerned that they may miss a window of opportunity for early surfactant, they can be directed to the intubation criteria for the early CPAP group. Much time was spent in protocol development with this section.

-----Original Message-----
From: Frantz, Ivan [mailto:IFrantz@tufts-nemc.org]
Sent: Friday, April 21, 2006 2:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Slide; SUPPORT

Do you have a copy of the slide showing publications by year from the network, and if so would you be willing to share it?

I am about to start the debate at our center about entering the SUPPORT trial. We are a strong early surfactant center and among my challenges will be to convince the group that even if there is not local equipoise, that there is equipoise in the bigger picture. Do you have a sense of how many sites sit on either side of the CPAP vs Surfactant issue as their standard practice prior to the start of SUPPORT. Old vs current vs new sites would all be interesting if you have the information, even if only informally.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: RE: Prospective meta analysis
Date: Friday, April 21, 2006 10:07:05 AM
Attachments: 2. NeOProM protocol - draft V5 22Mar06.pdf

Hi Wally and Rose
Here is the first draft of the proposal for the prospective meta analysis. The group is going to meet in San Francisco at the PAS, 10:00AM Sunday at the registration desk. If either of you would like to come, that would be great. I will keep you in the loop.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thu 4/20/2006 8:50 AM
To: Neil Finer; Wally Carlo, M.D.
Subject: RE: Kaiser: Permission to use statement

Hi, I have 13 yes votes to share out SUPPORT trial protocol information with Dr. Kaiser. The language has undergone some changes and I wanted you to look at it and make final suggestions.

Thanks to both of you for following this email trail!!!

Rose

Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing f CPAP started in the delivery room or following delivery vs. prophylactic surfactant in the first hour of life for premature infants born at 24 to 27 weeks gestation. This trial was preceded by a pilot study to assess feasibility of CPAP in the delivery room (Finer reference below). For the early CPAP group, one of the criteria that clinicians may use to discontinue CPAP and intubate infants is if their PaCO2 levels exceed 65 mm Hg . Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher PaCO2 levels in premature infants with the primary outcome being mortality and/or BPD at 36 weeks and a secondary outcome of neurodevelopmental impairment at 18-22 months corrected age."

Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL, Kandefer S. Delivery Room Continuous

Positive Airway Pressure/Positive End Expiratory Pressure (CPAP/PEEP) In Extremely Low Birth Weight

(ELBW) Infants; A Feasibility Trial. Pediatrics 2004 Sep;114(3):651-7.

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, April 19, 2006 3:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson

Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

Hi Rose

I like the term "CPAP started in the delivery or following delivery" since previous studies that have used CPAP have used the term early for CPAP started at 4 -12 hours.

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 19, 2006 6:12 AM
To: Shankaran, Seetha; Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

It is really "early CPAP" as some children are stabilized in areas adjacent to the DR. -

Neil - your thoughts??
Thanks
Rose

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Wednesday, April 19, 2006 9:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

Rose

Can we state CPAP initiated in the delivery room instead of early?

Thanks

Seetha

Seetha Shankaran, M.D.

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Wayne State University School of Medicine

Director, Neonatal-Perinatal Medicine

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Hutzel Women's Hospital

Tel 313-745-1436

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-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 18, 2006 12:17 PM
To: Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: FW: Kaiser: Permission to use statement

Hi,

Dr. Kaiser is requesting permission to use intubation criteria that were developed for the SUPPORT Trial in a chapter that he is currently writing. Please review the language and send me a YES/NO vote by April 21 to allow this use in a published chapter.

FYI - since the protocol is funded by federal dollars, one could go through the FOIA procedure to obtain the protocol as this degree of detail does not appear on the clinicaltrials.gov website. For new centers, usually, in a collaborative spirit, many of these types of requests have been honored by the steering committee.

Please comment on the language:

"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their PaCO2 levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher PaCO2 levels in premature infants with one of the primary outcome being mortality and a secondary outcome of neurodevelopmental status at 18-22 months corrected age."

Thanks

Rose

From: Kaiser, Jeffrey R [mailto:KaiserJeffreyR@uams.edu]
Sent: Tuesday, April 18, 2006 12:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Kaiser: Permission to use statement

Dr. Higgins,

Thanks for speaking to me today regarding a chapter I am writing for a textbook that is being edited by Dr. Michael Schimmel, Director of the NICU at Shaare Zedek Medical Center in Jerusalem. The title of the chapter is Neurological Sequelae Following Mechanical Ventilation, with a proposed subtitle "Neurological Sequelae of Extremes of Carbon Dioxide. I would like to get permission from the NICHD Neonatal Network Steering Committee to use the following sentences:

"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their PaCO2 levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher PaCO2 levels in premature infants with one of the primary outcomes including mortality and neurodevelopmental outcome at 18-22 months corrected age."

I am willing to have the sentences edited as per the Steering Committee.

Thank you for your time,

Jeff Kaiser

Jeffrey R. Kaiser, MD, MA

Associate Professor of Pediatrics and Obstetrics and Gynecology

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Confidential: not for circulation or quoting

Appropriate levels of oxygen saturation for extremely preterm infants: a prospective individual patient data meta-analysis

The **Ne**onatal **O**xygenation **Pro**spective **M**eta-analysis (**NeOProM**) Collaboration

DRAFT PROTOCOL

CORRESPONDENCE TO:

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Abstract

Background

Despite oxygen being one of the most commonly used therapies in the care of small or sick newborns, uncertainty regarding the most appropriate levels of oxygenation for extremely preterm infants has existed for over 50 years. It remains unknown whether the anticipated short term benefits (such as reduced respiratory and ophthalmic morbidity) of targeting oxygen saturation levels generally 'lower' from birth can be achieved without resulting in small, but important, increases in death and major disability rates for these vulnerable infants.

Methods/Design

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration has been formed to undertake a prospective individual patient data meta-analysis to answer this important clinical question. This approach is considered 'gold standard' of systematic review methodology. It provides the same strengths as a single large-scale randomised trial, but provides greater pragmatic flexibility, especially regarding the different regulatory and recognition needs that arise when multiple funding sources are required. This will be the first prospective meta-analysis undertaken in neonatology. Several randomised trials of similar design are now being planned and/or conducted worldwide. Together these trials plan to recruit approximately 6,500 infants which is a sufficient sample size to detect a difference in death and/or major disability of as little as 4%.

Progress to date

A collaborative group was formed in 2003. The first participating trial will commence enrolment in 2005. Final results should be ready for presentation to, and discussion with, the NeOProM Advisory Group in 2012 with the main publication is expected soon thereafter.

Background

Extreme prematurity (birth more than 12 weeks early at less than 28 weeks' gestation) affects approximately 1% of births.[1] These infants require costly care within a neonatal intensive care unit (NICU) and about 75% are discharged home alive.[2] Despite a life expectancy of 70 years, they sustain severe morbidity.[3] Their risk of chronic lung disease, poor growth, respiratory illness, hospital re-admissions, visual deficits, cerebral palsy, sensori-neural disability and cognitive, educational and behavioural impairment is higher than in term infants.[4] They account for most of the costs and disability from NICU care.[5] Their risk of visual deficit may be increasing.[6] Reducing these morbidities would enhance their quality of life and benefit their family and the community.[7]

Oxygen toxicity in very premature infants

Oxygen is the most common therapy used in the care of very premature infants. It has been associated with significant improvements in neonatal survival and disability.[8] However, these infants are highly sensitive to its harmful biochemical and physiological effects. While oxygen is essential for metabolism, its by-products - free radicals and reactive oxygen species - cause tissue injury. Toxic oxygen radicals are increased in hyperoxaemia (too much arterial oxygen)[9] and in re-oxygenation after hypoxaemia (too little arterial oxygen). Premature infants are vulnerable to oxidative stress because they lack antioxidant protection.[9] They lack plasma radical scavengers, such as Vitamin E or beta- carotene, antioxidant enzymes, such as glutathione peroxidase, and their red cells lack superoxide dismutase.

Hyperoxaemia can constrict or obliterate vessels in an immature eye and brain, causing ischaemic injury.[9] Less exposure to oxygen is a simple, logical strategy that could reduce oxidative stress and tissue injury and prevent morbidity in very premature infants. In healthy premature infants breathing air, arterial oxygen saturation is 85 - 98%, which is considered physiological. However, the optimum range of arterial oxygen to minimise organ damage, without causing hypoxic injury, is unknown.

How oxygen causes Retinopathy of Prematurity (ROP)

In early fetal life, the retina is avascular. Vessels grow out from the centre, controlled by vascular endothelial growth factor (VEGF), released by normal hypoxic retinal tissue. After premature birth, treatment with inspired oxygen may flood the retina with oxygen. When oxygen treatment stops, the ischaemic peripheral retina becomes severely hypoxic. There is abnormally high secretion of VEGF and new vessels and fibrous tissue proliferate and invade the vitreous. Fibrous contraction leads to retinal detachment and visual loss.[10] Destroying these proliferating vessels by ablative laser surgery can prevent retinal detachment. This saves central vision in some cases, but there is often residual visual loss. Of survivors <28 weeks' gestation, **50% have ROP, 12.5% have severe (Grade III/ IV) ROP,[2] 56% of these have surgery, but about 10% of those treated become blind**. New recommendations will result in more infants with severe ROP having laser surgery.[11] Of survivors of 28-29 weeks' gestation, <2% get severe ROP.[2]

Oxygen and lung disease

High inspired oxygen contributes to chronic lung disease (broncho-pulmonary dysplasia) which is associated with poor outcome.[12, 13] Improved survival has increased chronic lung disease, leading to poor growth, impaired neuro-development and greater health costs.

Oxygen and brain injury

As with any treatment, oxygen might increase disability by salvaging sick babies who would otherwise have died.[8] Oxygen may contribute to brain damage in premature infants, through oxidative stress and low cerebral blood flow. Oxidative damage to premyelinating oligodendrocytes in cerebral white matter is proposed as a mechanism of periventricular leukomalacia[14] - a form of white matter damage correlated with cerebral palsy. In premature infants, oxygen reduces cerebral blood flow velocity independently of the effects of hypocapnia or hypotension.[15]

These mechanisms may explain why hyperoxaemia was a risk factor for cerebral palsy in a study of 1105 preterm infants.[16] Hyperoxaemia in the first eight days was associated with twice the odds of cerebral palsy at 2 years, after adjusting for other variables. The adjusted odds of cerebral palsy increased eightfold for infants with the highest versus the lowest quintiles of exposure to hyperoxaemia, indicating a dose-response effect. Importantly, hyperoxaemia was defined as arterial oxygen above 60 mm Hg, in contrast with the long accepted upper limit of 80 mm Hg.[17, 18]

Previous trials of restricted or targeted oxygen in very premature infants

In a 2004 editorial in *Pediatrics*,[19] Dr William Silverman, formerly of Columbia University New York, states,

"...there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants. For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP-blindness, chronic lung disease and brain damage) was, and remains to this day, unknown."

The first case of ROP (originally called Retrolental Fibroplasia) was reported in 1942. By 1954, ROP had blinded about 10,000 infants.[19, 20] In 1954-56, 3 RCTs enrolling 341 infants proved that breathing unrestricted concentrations of inspired oxygen was a major cause of ROP.[21] Arterial oxygen levels were not measured, so the concentration of inspired oxygen could not be targeted to meet each baby's needs. To prevent ROP, all premature infants were restricted to breathing less than 40% inspired oxygen. In the next 20 years over 150,000 premature babies died of hypoxic respiratory failure.[8, 22-24] For every infant whose sight was saved, it is estimated that 16 died[8, 19, 22] and many others developed spastic diplegia.[23] The epidemic of blindness stopped – but at heavy cost. This might have been avoided had a larger RCT determined if oxygen restriction from birth increased or decreased death and disability.

The STOP ROP trial: The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity trial[25] used pulse oximetry to target lower (89-94%) or higher (96-99%) arterial oxygen saturation (SpO_2)[25] in 649 premature infants with early ROP. The higher range caused more adverse respiratory events, including pneumonia, chronic lung disease requiring oxygen and diuretic therapy.

The BOOST Trial: In the Benefits of Oxygen Saturation Targeting (BOOST) trial, reported in *New England Journal of Medicine*,[26] 358 infants born at less than 30 weeks' gestation were randomly assigned, *from ≥ 3 weeks after birth until they breathed air*, to target oxygen saturation (SpO_2) of 91-94% or 95-98%. This study aimed to decide if targeting higher SpO_2 improved growth and development. It did not, but higher SpO_2 did increase days of oxygen therapy and use of health care resources. Masked, adjusted oximeters were a major innovation. Half were adjusted to display masked values 2%

lower than actual SpO_2, the others displayed masked values 2% higher. Staff were unaware of actual SpO_2 and targeted a masked range of 93-96%. Masked oximetry was safe and acceptable to staff and parents. The authors concluded that RCTs are needed to determine how different SpO_2 levels *from the day of birth* affect ROP, chronic lung disease, growth, disability and mortality.[19, 26]

Current guidelines for levels of arterial oxygen to minimise the risk of ROP

A cohort study, reported in 1977, was unable to establish a relationship between arterial oxygen tension and retinopathy.[27] A range of 50–80 mm Hg became widely accepted,[17, 18, 28] but was based on professional consensus rather than fact. A later study confirmed that ROP occurred more often with arterial oxygen tension above 80 mm Hg,[29] but did not determine if another limit was safer. Oximeters measuring functional SpO_2 display values about 1.5% higher than those measuring fractional SpO_2.[30] Normal fetal oxygen saturation is 70–80%.[31, 32] In transposing oxygen tensions of 50–80 mm Hg into equivalent arterial oxygen saturation, most clinicians have targeted functional SpO_2 90–95% (the mid range of what is considered physiological) with a minimum of 85%.[33]

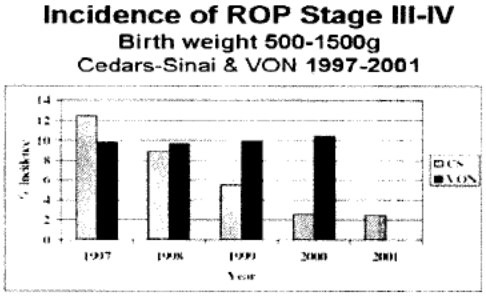
Four recent cohort studies of lower oxygen saturation targets in relation to short-term outcome

1. Tin showed that lower SpO_2 correlated with improved outcomes in infants <28 weeks' gestation.[32] Alarm limits for SpO_2 in four NICUs ranged from 70–90% to 88–98%. Babies in the NICU targeting SpO_2 70-90% had less ROP surgery than those in the NICU targeting SpO_2 88-98% (6.2% *v* 27.2%: 80% relative risk reduction (RRR), p < 0.01). Survivors were ventilated less often (13.9 *v* 31.4 days), fewer needed oxygen at 36 weeks' postmenstrual age (18% *v* 46 % (61% RRR), and fewer were below the 3rd centile for weight at discharge (17% *v* 45%, 62% RRR) (all p< 0.01) while survival (52% *v* 53%) and cerebral palsy (15% *v* 17%) at one year were similar.[32]

2. Anderson reported less Grade III/ IV ROP (2.4% vs. 5.5%, p<0.001) and less ROP surgery (1.3% v. 3.3%, 61% RRR, p<0.037) in NICUs with functional SpO_2 upper limit ≤ 92% vs >92%.[34]

3. Sun studied 1544 infants weighing <1000 g in NICUs with upper limit SpO_2 of ≤95% vs >95%. NICUs with ≤95% limits had less Grade III ROP (10% vs 29%), surgery (4% vs 12 %, 67% RRR), chronic lung disease (27% vs 53%, 49% RRR) (all P< 0.001) and similar mortality (17% vs 24%).[35]

4. Chow[36] found that 83-90% functional SpO_2 was associated with less Grade III-IV ROP than 90 - 98% in historical controls. From 1998 to 2001, it fell from 12.5% to 2.5% (80% RRR, p= 0.01) and ROP surgery fell from 7.5% (6/80) to zero (0/188) (100% RRR, p=0.0006). Fewer infants had Grade III/ IV ROP than in the Vermont Oxford Quality Improvement Network (VON) (Figure to right).



These 4 studies strongly suggest that lower SpO_2 may reduce ROP surgery by 61-100%; chronic lung disease by 49 – 61%; and poor growth by 62%. Effects on mortality and sensori-neural outcome could be beneficial or harmful.

The unresolved question regarding appropriate levels of oxygen saturation

There are two opposing concerns. Less inspired oxygen (to target SpO_2 <90%) may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development.[37-39] More inspired oxygen (to target SpO_2 >90%) may increase severe ROP and chronic lung disease.[16, 32, 34-36] After recent studies,[32, 34-36] more NICUs are adopting lower SpO_2. This trend may increase before the risks and benefits are determined. The disastrous mistakes of the 1950s[17, 19, 20, 22, 24] show how rapidly opinions can shift, destroying the chance of reliable evidence.

Current developments: formation of the international NeOProM Collaboration

Worldwide demands to resolve the dilemma are intensifying. In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct the NeOProM (Neonatal Oxygenation Prospective Meta-analysis) Collaboration. The group has members in Australia, NZ, US, Canada, UK and elsewhere in Europe who interact frequently via email, teleconferences and at international meetings. Since July 2003, members have addressed over 20 national or international meetings. In December 2003, the NeOProM project was outlined in a commentary in *Pediatrics*.[40]

Several NeOProM Collaboration members have been successful in seeking support from their respective national funding agencies to conduct individual trial in their own countries, with a common core protocol and dataset, which will contribute to the prospective meta-analysis of all trials. Successful funding submissions have been awarded in Australia, Canada, New Zealand, USA and UK. One further planned trial in the USA will submit a funding application in 2007. See Appendix 1 for the listing of potential included trials.

Establishing the first Prospective Meta-Analysis (PMA) in neonatology: a major step forward

Each of these planned trials will recruit over a thousand babies, and will thus yield a great deal of useful information in their own right. However, none individually will be able to exclude the possibility that valuable short term benefits associated with giving babies less oxygen are not associated with a small but significant ***increase*** in death or serious neurosensory disability in survivors.

For example, the recently funded Australian BOOST-II trial which plans to recruit approximately 1,200 infants will be able to exclude a clinically important difference of 8% (from 37% to 45% or from 37% to 29%) in the major composite outcome of death or severe disability. This would mean one less infant would died or be disabled for every 12 given less oxygen. A smaller difference of 4% is also important as it would mean one less major outcome for every 20 infants given less oxygen. However, excluding a 4% difference requires approximately 6,500 infants, which no single country can recruit.

For this reason, the Principal Investigators planning these trials around the world have pledged their support for a prospective meta-analysis (PMA) of individual patient data from each of these studies. Combining the results from several trials of similar design using prospective meta-analysis methodology differs from a standard meta-analysis of trial results in several important ways.

Key features of prospective meta-analysis

A prospective meta-analysis (PMA) is a meta-analysis where studies (usually randomised controlled trials) are identified, evaluated, and determined to be eligible before the results of included studies are known or published. This methodology can help avoid some of the potential biases inherent in standard, retrospective meta-analyses. These can include publication bias (where studies with more positive results are more likely to be published and thus are more likely to be included in the analysis); selection bias of subjects and trials; and bias due to *post hoc* selection of study questions, eligibility criteria, outcome definitions or subgroups.[41]

The key features of PMA are to prospectively define and clearly specify the objectives, research question(s), specific aims, hypotheses, subject eligibility criteria, subgroups, predictors, outcomes (primary and secondary) and the analysis plans of eligible studies in advance of knowing or publishing individual trial results.[42] PMA provides more reliable estimates of treatment effects through prospectively planned combined analysis of large-scale randomized controlled trials. In addition to having greater power to detect meaningful modest differences in less frequent, clinically important outcomes, PMA provides adequate power to evaluate events in important subgroups underrepresented in smaller RCTs. Thus, PMA provides the same strengths as a single large-scale randomised study.

Another advantage is that PMA provides greater, pragmatic flexibility in achieving the objectives of a single mega-trial. Funding agencies often have different funding cycles, requirements, regulations and justifiable recognition needs. Through prospectively planned combined analysis of large, randomised trials, PMA accommodates funding agency variations, reduces costs to an individual funding agency for a mega-RCT, while providing the same strengths and benefits of a single mega-randomised study. In this regard, PMA sets an important precedent for future large neonatal trials. PMAs establish uniformity in common protocol among trials, data collection, outcomes, and rules whilst permitting flexibility in pre-specified protocol details and funding regulations. To protect the integrity of each individual trial, the main results are published in the group name and only after the principal results of each individual trial have been published. This method also has the flexibility to allow questions to be added after the PMA protocol has been developed provided the additional studies or questions are chosen in a manner masked to the results.

By establishing a collaboration between trialists of eligible studies, it is possible to collect individual patient data (IPD) and incorporate it into the meta-analysis. Using data collected from each individual within a trial, rather than relying on aggregate data from each trial, can improve the power and scope of the meta-analysis. In particular, a meta-analysis using IPD can enable more flexible and detailed sub-group analyses.[43, 44]

There are, however, some issues that require particular attention when using prospective meta-analysis methodology. These include ensuring the scientific integrity of both the individual trials and the PMA are maintained; reaching consensus on the goals of the PMA, what data to collect, how and when to collect them and how to maintain uniformly high quality data across all sites; defining the role of each of the Data Coordinating centres; defining if and how each of the trial's Data Monitoring Committees will interact and share findings; and establishing policies concerning analyses of the pooled data, publication of pooled analyses, and ownership of the pooled database.

Previous experience with prospective meta-analysis

This will be the first-ever neonatal prospective meta-analysis. However, the methodology has been used extensively in other areas of health care, particularly in cardiovascular disease and cancer. Examples of this approach include two major prospective meta-analyses of cholesterol-lowering treatments (PPP and CTT).[41,45] PPP was a prospectively planned combined analysis of three large-scale pravastatin trials over a minimum of 5 years. PPP contains data for over 19,500 patients and has the power to examine the effects of treatment on various mortality and cancer outcomes as well as the ability to evaluate important events in subgroups under-represented in previous trials.[45] The CTT Collaboration[41] is a prospective meta-analysis of 14 randomised trials of evaluating a fibrate or dietary modification on cholesterol levels. The CTT Collaboration has information on over 90,000 patients. These large PMAs provide more reliable estimate of the effects of cholesterol reduction on cause-specific mortality and of the effects on coronary mortality within important subgroups. The Blood Pressure Lowering Treatment Trialists Collaboration recently published[46] the results of a series of seven sets of prospectively-designed overviews that assessed the comparative effects of different blood-pressure lowering regimens on major cardiovascular results. These meta-analyses included data from 29 randomised trials and over 162,000 people and were able to establish conclusively the differential effects of different drug regimes on cause-specific cardiovascular outcomes.

The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration will be coordinated by Dr Lisa Askie under the supervision of Professor John Simes in Sydney, Australia. Dr Askie was the lead author of BOOST trial publication[26] and has considerable experience in neonatal Cochrane reviews.[21, 47-49] She has recently spent two years at the UK Cochrane Centre in Oxford (with Professor Mike Clarke)[44] and the MRC in London (with Dr Lesley Stewart)[43] gaining expertise in individual patient data meta-analysis methods as a NHMRC Sidney Sax Postdoctoral Fellow. Professor Simes is the world's leading authority on prospective meta-analysis methodology.[41] The NeOProM protocol will be submitted to the Cochrane Collaboration Neonatal Review Group, and both the Cochrane Prospective Meta-Analysis Methods Group (co-convened by Prof Simes) and the Cochrane Individual Patient Data Methods Group (co-convened by Dr Lesley Stewart) will be notified and consulted for methodological advice as required. The Principal Investigators of each of the trials involved in NeOProM will be members of the Collaboration's Management Committee (see *Project Management*). Thus, this is an opportunity to adapt the methodologies of prospective meta-analysis and individual patient data meta-analysis, already well-established in other health care fields, for use in answering important neonatal questions.

Study design

Objectives

The primary objective of the NeOProM Collaboration is to meta-analyse data from several randomised trials to address scientific questions for which there may be inadequate power within individual studies.

The primary question to be addressed by this study is: Does less oxygen given to extremely preterm infants from birth or soon after, increase or decrease the composite outcome of death and major disability by 4% or more? NeOProM will have the statistical power to detect important risks or benefits in potentially conflicting secondary outcomes.

Hypotheses

Compared with functional oxygen saturation level (SpO_2) of 91-95%, targeting SpO_2 85-89% within 24 hours of birth, for a minimum of two weeks and thereafter until the infant reaches 36 weeks postmenstrual age (pma) or breathes air (whichever is achieved first), is associated with:

Primary hypothesis: <4% absolute risk difference from 42%[4,5] to 46% or from 42% to 38% (10% relative risk increase or 10% relative risk reduction (RRR)) in mortality and major disability at 2 years postmenstrual age (defined as gestational age plus chronological age).

Hypothesis 2: 2.4% absolute risk reduction (ARR) from 7%[2] to 4.6% (34% RRR) in ROP surgery.[11]

Hypothesis 3: (a) 10% ARR from 40%[2] to 30% (25% RRR) in risk of being treated with oxygen or on respiratory support at 36 weeks postmenstrual age; (b) fewer days being ventilated through an endotracheal tube; (c) fewer days of supplemental oxygen; (d) fewer infants discharged on home oxygen; (e) fewer deaths after more than 4 weeks of age attributed to pulmonary causes.

Hypothesis 4: (a) better weight gain between birth and 36 weeks postmenstrual age
(b) better head growth and weight gain between birth and 18-24 months postmenstrual age
(c) no increase in (i) treated patent ductus arteriosus or (ii) surgery for necrotizing enterocolitis

Sample size

A total sample size of 5230 (SUPPORT, BOOST II Aus, BOOST II NZ, BOOST II UK, COT) would have a 90% power to detect the differences in outcome in hypothesis 1, and power to detect even smaller differences that those outlined in hypotheses 2 and 3. With the addition of a further trial (US POST) the total sample size would increase to 6450. This would further increase the precision of the results by ensuring that a 4% increase in death or major disability could be detected (for example from 42% to 46%), with 95% confidence that the true result was an increase in this outcome from 42% to between 43.7% and 48.7% (RR1.10, 95% CI 1.04-1.16) - see Figures 1-3.

Figure 1: Sample NeoProM PMA result – increase in death or major disability of 4% (from 42% to 46%) in lower SpO2 target range group, for total sample size of 6450 infants

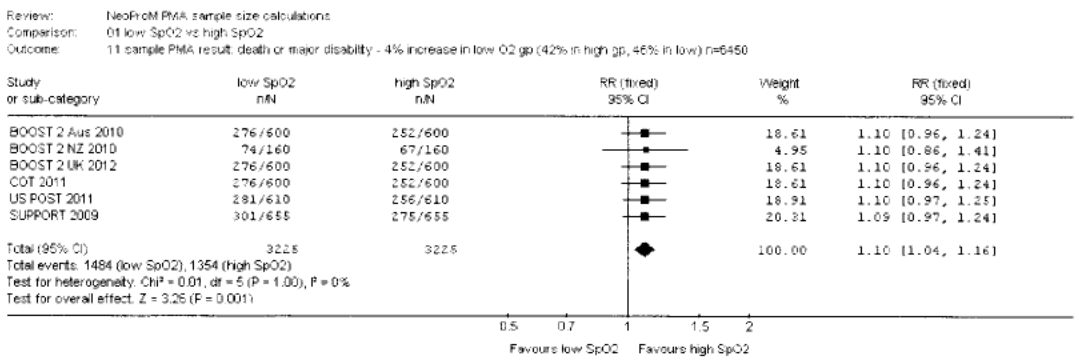


Figure 2: Sample NeoProM PMA result – decrease in ROP surgery of 2.4% (from 7% to 4.6%) in lower SpO2 target range group, for total sample size of 6450 infants

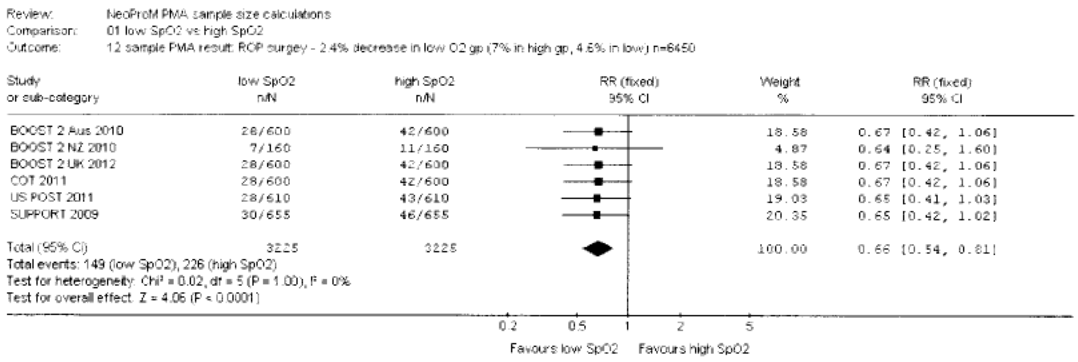
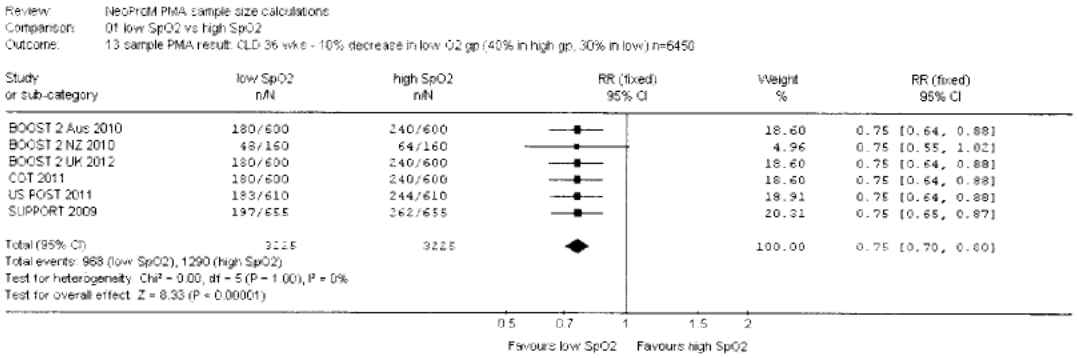


Figure 3: Sample NeoProM PMA result – decrease in CLD at 36 weeks of 10% (from 40% to 30%) in lower SpO2 target range group, for total sample size of 6450 infants



Identifying studies

The NeoProM Secretariat will be responsible for identifying potentially eligible studies. These are to be identified prospectively by a range of methods, including computer-aided literature searches of relevant bibliographic databases (such as MEDLINE and *The Cochrane Controlled Trials Register)*, manual searches of relevant journals, scrutiny of the reference lists of trials and review articles, scrutiny of abstracts and meeting proceedings, scrutiny of the relevant trial registers, and by inquiry among colleagues, collaborators and manufacturers of pulse oximeters. This will be undertaken at least twice per year. The Secretariat will be responsible for maintaining a register of eligible trials. Once a potentially eligible trial is identified, the investigators will be contacted, sent a copy of the NeoProM protocol and information describing the study will be sought. Newly identified studies will be included in the meta-analysis, provided they are registered before their results are known. Appendix 1 lists the currently registered eligible trials.

Eligibility criteria for studies to be included

The eligibility criteria for the types of study designs, participants, interventions, outcomes and other features of the studies to be included in the meta-analysis are listed below. Each potentially eligible study will be assessed independently by two members of the Secretariat, unblinded to the trial's identity. Any differences of opinion regarding the assessment of the eligibility criteria will be resolved by discussion between the two assessors. If differences cannot be resolved, a third member of the Secretariat will be asked to assess the study. If individual patient data are unavailable from an eligible trial, the trial will remain included in the meta-analysis and aggregate data used where possible.

a. Study design

Studies will be included if they were randomised trials. Quasi-random study designs, such as those using alternate allocation, will be excluded. The level of allocation concealment within each trial will be assessed according to the criteria outlined in the Cochrane Handbook,[42] and only those trials with adequate allocation concealment will be eligible. Once the individual patient data is received from each trial, further assessments of the pattern of randomisation will be made via thorough data checking procedures.

b. Participants

Participants in the eligible trials will be infants born before 28 weeks' gestation and enrolled within 24 hours of birth.

c. Interventions

The interventions will be random assignment to either a lower (SpO_2 85-89%) or higher (SpO_2 91-95%) oxygen saturation target range, for an initial two week period, and thereafter until breathing room air or until at least 36 weeks postmenstrual age, whichever occurs first. Intervention assignment must be masked to parents, care-givers and outcome assessors by the use of MASIMO Signal Extraction Technology© pulse oximeters that have been adjusted to display either 3% above or below the infant's actual saturation value, within the 85-95% oxygen saturation range. Enrolled infants will be required to use the allocated trial oximeter for a minimum of two weeks, even if not requiring supplemental oxygen. Randomised trials with factorial designs that incorporate other intervention comparisons will be eligible.

d. Outcomes

Eligible trials must collect the core data items listed to follow. This list of core data items has been compiled following extensive consultation with the principal investigators of all known eligible trials, but is still under discussion and not finalised as yet. Eligible trials may choose to collect additional data items that will not be included in the PMA. More detailed definitions for the data items listed below can be found in Table 1. Details of the suggested coding for each of the following variables will be found in Appendix 2 (currently under development).

a. Characteristics of the trial

1 informed consent obtained
2 dates trial opened and closed to accrual
3 total number of infants randomised
4 treatments used in each arm of the trial
5 intended duration of treatments
6 definitions of key outcomes used in the trial
7 method of random allocation
8 stratification factors used
9 methods of allocation concealment

b. Characteristics of enrolled infants at trial entry

1 unique identifier for the enrolled infant, coded for anonymity
2 date and time of birth
3 gestational age at birth, or best estimate of expected date of delivery or date of mother's last menstrual period
4 date and time of randomisation
5 date and time intervention commenced
6 respiratory support immediately prior to intervention commencement
7 inborn or outborn status
8 antenatal corticosteroids
9 mode of delivery
10 weight at birth
11 gender
12 singleton or multiple birth
13 5 minute Apgar score

c. Infant data at 36 and 40 weeks postmenstrual age

1 weight
2 FiO_2 or rate of nasal flow oxygen
3 other measures of respiratory support

d. Infant data at discharge from hospital

1 total days with endotracheal or tacheostomy tube
2 total days of CPAP
3 date and gestational age when last received supplemental oxygen
4 date and gestational age when trial intervention ceased
5 surfactant treatment
6 PDA requiring treatment
7 NEC
8 postnatal steroids for lung disease
9 major cerebral abnormalities on cranial ultrasound
10 ROP outcomes: maximum grade, treatment with oxygen or surgery
11 care in non-tertiary unit prior to discharge
12 date and gestational age at discharge home
13 discharge home on supplemental oxygen
14 death before hospital discharge

e. Child data at 18-24 months corrected age

1 death between hospital discharge and 18-24 months corrected age
2 Bayley developmental assessment scores
3 visual outcomes
4 hearing outcomes
5 cerebral palsy
6 growth measures
7 re-admissions to hospital up to 18-24 months corrected age

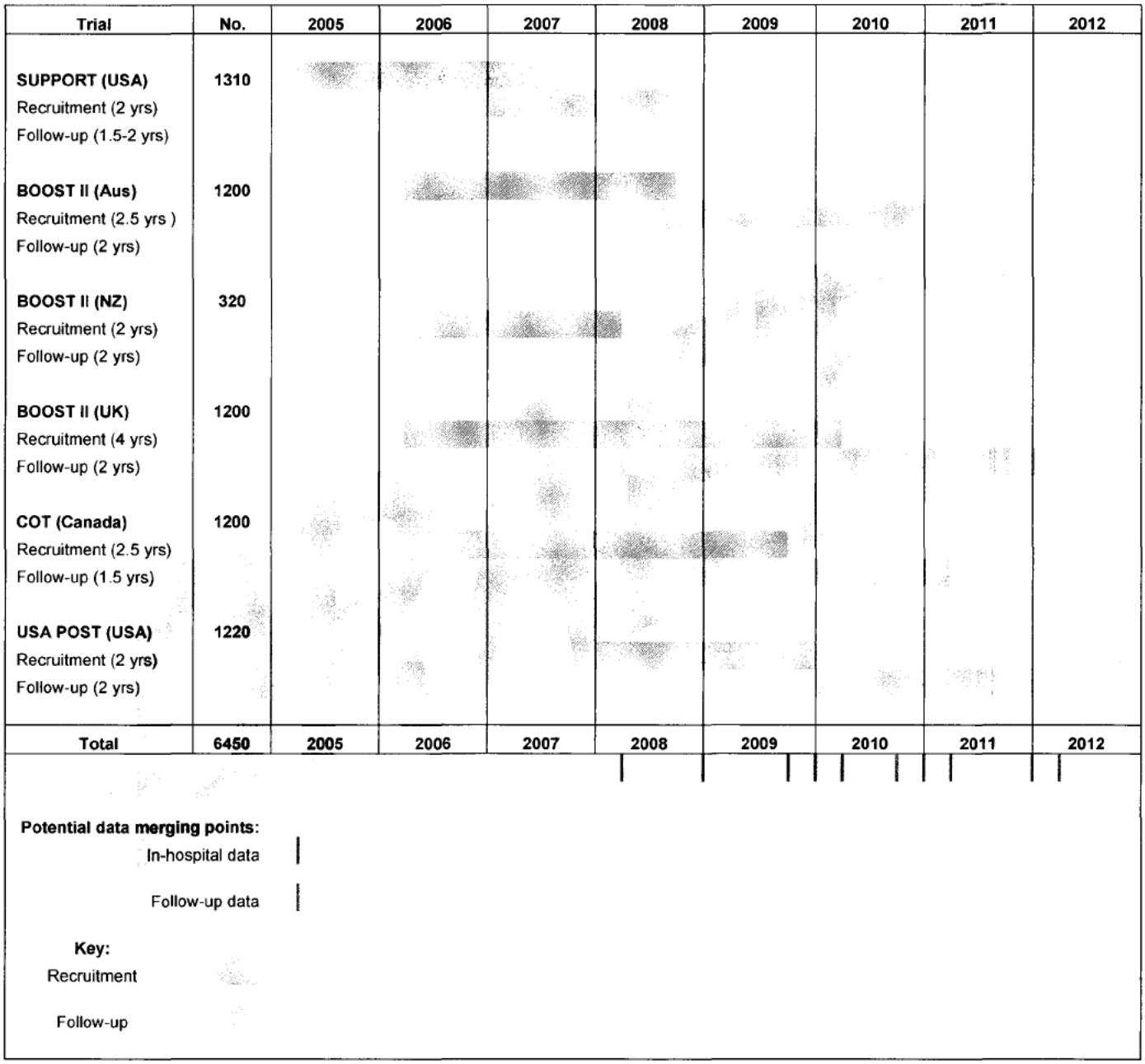
Data collection, data management and confidentiality

The individual patient data provided by the NeOProM Collaborators will be de-identified, re-coded as required and stored in a custom-designed database. It will not include any patient identifying information such as names or addresses. Data will be stored at the NeOProM Data Coordinating Centre. Electronic data will be located on a secure, password protected network server. Copies of any hardcopy data will be stored in locked filing cabinets until converted into electronic format, and will then be securely destroyed. Only authorised personnel will have access to the data. All data will be securely stored and archived according to the policies of the major funder(s).

The data provided for infants in each trial will be checked with respect to range, internal consistency, consistency with published reports and missing items. Trial details such as randomisation methods, and timing of the interventions will be cross-checked against any published reports, trial protocols and data collection sheets. Integrity of the randomisation process will be examined by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of prognostic factors across treatment groups (taking into account stratification factors). Inconsistencies or missing data will be discussed with the individual trialists and attempts will be made to resolve any problems by consensus. Each trial will be analysed individually, and the resulting analyses and trial data will be sent to the trialists for verification.

Data will be sought from each trial at prospectively specified intervals as outlined below. The date by which hospital-based outcomes and longer-term followup results will emerge from the studies will guide the timetable for seeking data from individual trialists. Trial data submitted to the NeOProM Secretariat will be held in strict confidence and will not be used in any publication without the permission of the responsible trialists. Particular care will be taken to ensure that the data collection and analysis procedures do not compromise any of the individual trials.

Proposed timetable for NeOProM data collection and receipt



Data monitoring procedures

Prospectively collected, de-identified (groups randomly labelled A and B, rather than lower or higher SpO_2), accumulating summary data will be made available to the participating trials Data Monitoring Committees and the NeOProM Advisory Group at pre-specified timepoints that have yet to be decided. The data items to be made available to individual trial Data Monitoring Committees will also be pre-specified, but yet to be decided. The NeOProM Advisory Group will consult and decide on these procedures prior to the first potential data merging timepoint (see proposed timeline page 14). The chairpersons of each of the ongoing individual trial Data Monitoring Committees and members of the NeOProM Advisory Group will meet (via teleconference) following each data receipt timepoint for discussion of the de-identified, accumulating summary data.

Because different oxygen targets may have competing risks, it is essential that sufficiently large numbers of recruits are allowed to accumulate to be able to demonstrate net clinical benefit or harm. That is, evidence of net clinical benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment to the prospective meta-analysis because of a 3% reduction in severe ROP in the lower oxygen group, before the project had accumulated sufficient power to exclude a 4% increase in mortality or severe neuro-developmental impairment in the same group.[50-54]

Planned analyses

This section contains a summary of the planned analyses. The full, detailed analysis plan will be discussed and agreed upon by the NeOProM Collaborators before any data have been analysed. The detailed analysis plan will be made available in a separate document.

Analysis will be of all infants ever randomised and will be based on intention-to-treat. In the main analyses a two stage approach will be taken. Outcomes will be analysed in their original trial and then these separate results will be combined to give an overall measure of effect. A fixed effect model will be used and the assumption of homogeneity of treatment effects will be tested using the chi squared test. The I^2 statistic will also be used to assess consistency of results.

1. Outcomes to be analysed

The main analyses comparing targeting a lower oxygen saturation range (SpO_2 85-89%) with a higher one (SpO_2 91-95%) will be undertaken for all outcomes listed below.

a. Primary outcome

- composite outcome of death or major disability by 18-24 months postmenstrual age (gestational age plus chronological age). Major disability is any of the following: Bayley Developmental Assessment MDI score <70 (-2SD), severe visual loss (cannot fixate or is legally blind (<6/60) in both eyes), cerebral palsy with inability to walk at 18-24 months postmenstrual age, or deafness requiring hearing aids.

b. Secondary outcomes

- retinal surgery (performed if Type I ROP or threshold ROP occurs[10])

- duration of oxygen therapy, defined as (a) oxygen at 36 weeks postmenstrual age, (b) days of endotracheal intubation (c) days of CPAP, (d) days of oxygen, (e) days on home oxygen
- oxygen requirement at 40 weeks postmenstrual age
- patent ductus arteriosus diagnosed by ultrasound and requiring medical or surgical treatment
- necrotising enterocolitis requiring surgery
- weight at birth, 36 weeks, discharge home and 18-24 months corrected age
- retinal structure at one year or when last seen
- re-admissions to hospital up to 18-24 months postmenstrual age
- cerebral palsy and unable to walk at 18-24 months postmenstrual age
- blindness (<6/60 vision)
- deafness requiring hearing aides
- mean Bayley MDI and PDI scores
- death after 4 weeks chronological age attributable primarily to pulmonary causes

2. Planned sub-group analyses

The effect of the intervention (higher or lower oxygen saturation targeting) may be differential due to certain characteristics of either the infant or the way the intervention was delivered (for example, timing of commencement or cessation). These possible effects will be explored by the following sub-group analyses.

a. Patient-level characteristics

- gestational age (<26 weeks / ≥26 weeks)
- surfactant treatment
- inborn or outborn status
- SpO_2 lability

b. Intervention-level characteristics

- time of intervention commencement (≤6 hours / >6 hours)
- time of intervention cessation (until breathing room air or at 36 weeks postmenstrual age whichever occurs sooner / until breathing room air or at discharge home whichever occurs sooner / until breathing room air irrespective of intervention cessation date - including infants receiving the intervention at home)

3. Planned sensitivity analyses

To assess whether results are robust to different methods of analysis the following sensitivity analyses will be conducted:

- comparison of analyses using random effects and fixed effect models

4. Additional analyses

Depending on what data are available, the level of heterogeneity encountered and available time a one-stage modeling approach may also be undertaken to further explore important key outcomes as appropriate.

Ethical considerations

Participants in the individual trials have previously given informed consent to participate in their respective trial. The data for this project are to be used for the purpose for which they were originally collected and are available through an agreement between all trialists of the NeOProM Collaboration. These trialists remain the custodians of their original individual trial data at all times and have the right to withdraw some all or of their data from the analyses. Data are provided on the stipulation that all trials have received ethical clearances from their relevant bodies.

Project management

Membership of the NeOProM Collaboration will include representative(s) from each of the trials contributing data to the project with an accompanying project coordination and data management structure as described in this section. The membership and responsibilities of each of these management groups is as follows:

a. Secretariat

The Secretariat will be responsible for day-to-day project management decisions and will meet approximately 4-6 times per year, usually via teleconference. Membership: L Askie[1] (co-chair, project co-ordinator), C Cole[2] (co-chair), J Simes[1], W Tarnow-Mordi,[3] N Oden,[4] project administrator (yet un-named, located at [1 and/or 2]), A Ghadge,[1] trial coordinators for UK, US, Canadian, New Zealand and any other included trials.

[1] NHMRC Clinical Trials Centre, University of Sydney, Australia;
[2] Beth Israel Deaconess Medical Center, Boston, USA;
[3] Neonatal Intensive Care Unit, Westmead Hospital, Sydney, Australia;
[4] EMMES Corporation, Rockville, Maryland, USA.

b. Advisory Group

In addition to members of the Secretariat, all principal investigators of eligible trials will be contacted and invited to become members of the NeOProM Advisory Group. The aim of the Advisory Group is to facilitate representative input from the participating trialists. Membership of the Advisory Group may also include other international experts, invited by the Secretariat. The Advisory Group will communicate regularly via email, and will meet at least twice per year either in person or by teleconference. Membership (in addition to the above-named members of the Secretariat): D Henderson-Smart, J Sinclair, R Soll, D Ghersi, L Stewart, C Morley, P Davis, L Doyle, B Darlow, E Hey, P Brocklehurst, W Tin, H Halliday, B Schmidt, N Finer, D Phelps, N Paneth, A Lindblad, W Hay, and other members as deemed appropriate by the NeOProM Secretariat.

c. Project coordination and data management centre

The project will be coordinated from the NHMRC Clinical Trials Centre, University of Sydney, NSW, Australia. The coordination and data management centre will be responsible for the daily management of the project including correspondence, newsletter production, maintaining current trialist contact information, meeting / teleconference organisation, as well as the receipt, storage, and analysis of project data as directed by the Advisory Group.

d. Collaborators' meetings

All members of the NeOProM Secretariat and Advisory Groups will be invited to attend regular Collaborators' meetings. These meetings will be scheduled, where possible, to coincide with the annual Society for Pediatric Research conferences in the USA. The meetings will be designed to allow maximum input from the participating trialists into the design, conduct, analysis and reporting of the project's results.

At key stages of the data collection and analysis process, 'free-standing' Collaborators' meetings will be held. At these meetings the project results, data analysis issues and publication plans will be presented for discussion. Previous experience with other individual patient data and prospective meta-analysis projects have indicated that such meetings are very important for effective communication, timely data collection and meaningful interpretation and dissemination of results in these large, collaborative projects. The dates for Collaborators' meetings will be set by the Secretariat, in consultation with the Advisory Group.

Funding

Funding for the NeOProM Collaboration will be sought from national medical research agencies known to be supportive of large, collaborative, multinational projects and who have experience is funding this type of research methodology. This may include the National Health and Medical Research Council (NHMRC) of Australia, the UK Medical Research Council, the National Institutes of Health (USA) and others. Additional support will be provided by the various institutions to which members of the Secretariat and Advisory Groups belong. This project is being conducted independently of any commercial organisations.

Publication policy

Each of the participating trials will be able to publish their individual results prior to publication of the final PMA results. Once the results of each of the participating trials are available in the public domain, the results of the combined PMA will be presented to, and discussed with, members of the NeOProM Collaboration. The main manuscript will be prepared by the Secretariat, and then circulated to the Advisory Group for comment and revision. The revised draft paper then will be re-circulated to all members of these Groups for comment before publication. All publications using these combined data will be authored in the name of the NeOProM, as follows: the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration, with the names of the collaborating trialists listed separately elsewhere in the manuscript.

Summary

Despite oxygen being one of the most commonly used therapies in the care of small or sick newborns, uncertainty regarding the most appropriate levels of oxygenation for extremely preterm infants has existed for over 50 years. It remains unknown whether the anticipated short term benefits (such as reduced respiratory and ophthalmic morbidity) of targeting oxygen saturation levels generally 'lower' from birth can be achieved without resulting in small, but important, increases in death and disability rates for these vulnerable infants.

The NeOProM Collaboration has been formed to undertake a prospective individual patient data meta-analysis to answer this important clinical question. This approach is considered 'gold standard' of systematic review methodology. It provides the same strengths as a single large-scale randomised trial, but provides greater pragmatic flexibility, especially regarding the different regulatory and recognition needs that arise when multiple funding sources are required. This will be the first prospective meta-analysis undertaken in neonatology. Several randomised trials of similar design are now being planned and/or conducted worldwide. Together these trials plan to recruit approximately 6,500 infants which is a sufficient sample size to detect a difference in death and/or major disability of as little as 4%. The first participating trial commenced enrolment in 2005. Results should be ready for publication by 2012.

Appendix 1
List of potential eligible trials and their characteristics

Appendix 2
Suggested coding for core dataset variables (under development, not yet finalised)

Competing interests
None declared.

Acknowledgements
In addition to the named members of the NeOProM management groups, the following people have contributed to the success of the Collaboration: William Silverman, Iain Chalmers.

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Table 1

Key definitions for enrolment characteristics and outcomes measures

Enrolment characteristics	Definition
inborn / outborn status	infant born at a hospital with neonatal intensive care facilities (inborn) or at a hospital without neonatal intensive care facilities (outborn)
age at intervention commencement	age (in minutes, hours) after birth when the study oximeter was placed on the infant and thus the targeting of the allocated saturation target range was commenced
Primary outcome components	**Definition**
mortality	death before 18-24 months corrected age follow-up; cause of death category
neuro-developmental delay	Bayley Developmental Assessment MDI score <70 (-2SD),
severe visual loss	cannot fixate or is legally blind (<6/60) in both eyes
cerebral palsy	inability to walk at 18-24 months postmenstrual age
deafness	requiring hearing aids in either ear
Secondary outcomes	**Definition**
retinal surgery	laser or cryotherapy used for ROP treatment
maximal ROP stage before discharge	using International Classification of Retinopathy of Prematurity definitions
ROP treatment with oxygen therapy	prescription of high range oxygen saturation targeting for a short period to arrest the progression of pre-threshold ROP
duration of oxygen therapy	postmenstrual age when supplemental oxygen no longer required
patent ductus arteriosus	diagnosed by ultrasound and requiring medical or surgical treatment
necrotising enterocolitis	radiological diagnosis, clinical history plus either pneumatosis intestinalis, or portal vein gas, or a persistent dilated loop on serial X-rays
age at intervention cessation	postmenstrual age when targeting the allocated oxygen saturation range ceases
major cerebral abnormality	ventriculomegally, intraparenchymal echodense lesion, porencephalic cysts, cystic periventricular leukomalacia, cortical atrophy no resolved post-discharge

Appendix 1

List of registered eligible trials as at October 2005

1. Eligible trials: funded

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication
SUPPORT	USA	1,310	April 2005	June 2007	Dec 2008	June 2009
BOOST-II	Australia	1,200	Mar 2006	Sept 2008	Dec 2010	Apr 2011
BOOST-II	NZ	320	Mar 2006	Mar 2008	June 2010	Sept 2010
BOOST-II UK	UK	1,200	April 2006	April 2010	April 2012	Dec 2012
COT	Canada	1,200	Aug 2006	Aug 2009	Feb 2011	June 2011

2. Eligible trials: funding applications submitted

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication

Nil further at this time.

3. Eligible trials: funding applications in preparation

Trial acronym	Country	Planned n	Recruitment start date	Recruitment finish date	Follow-up data finalised	Planned date of publication
US POST	USA	1,220	to be determined: plans for funding re-submission underway			

Appendix 2

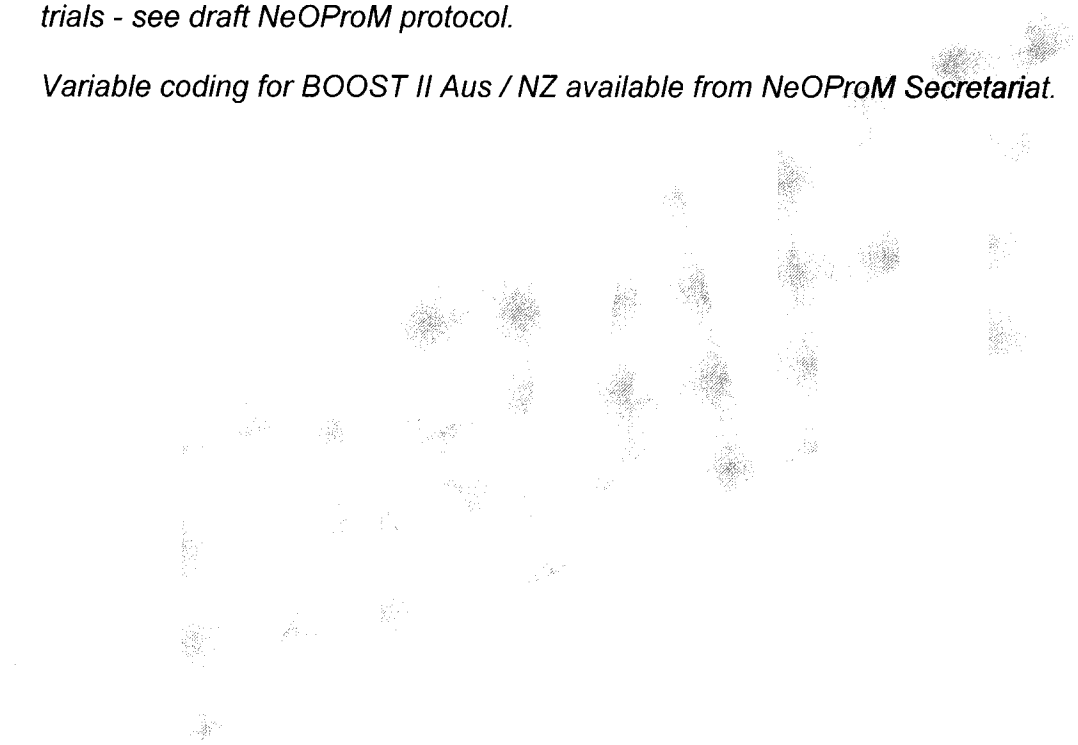
Suggest coding for core dataset variables

under development, not yet finalised

Detailed coding of the core NeOProM dataset will be finalised in consultation with full NeOProM Advisory Group once established.

However, common key endpoints have been agreed, in principle, across all participating trials - see draft NeOProM protocol.

Variable coding for BOOST II Aus / NZ available from NeOProM Secretariat.



From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: RE: Kaiser: Permission to use statement
Date: Thursday, April 20, 2006 1:12:53 PM

Hi Rose
IO would remove prophylactic as the studies reviewed as prophylactic gave surf at < 15 min. I think stating that we give in the first hour is appropriate or as Wally previously suggested prophylactic/early.
There was an f before the word CPAP which I removed. I would also remove the phrase "or following delivery" as the intent is deliver CPAP in the delivery room. I think my previous comment did not include an or so that I may have created this wording – I would leave it as CPAP started in the delivery room vs. surfactant
There are really 2 co-primary outcomes in view of the factorial design – I'm not sure that we need that amount of detail as this paragraph does not refer to the oximeter arm.
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 20, 2006 8:51 AM
To: Neil Finer; Wally Carlo, M.D.
Subject: RE: Kaiser: Permission to use statement

Hi, I have 13 yes votes to share out SUPPORT trial protocol information with Dr. Kaiser. The language has undergone some changes and I wanted you to look at it and make final suggestions.

Thanks to both of you for following this email trail!!!

Rose

Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing CPAP started in the delivery room vs. surfactant in the first hour of life for premature infants born at 24 to 27 weeks gestation. This trial was preceded by a pilot study to assess feasibility of CPAP in the delivery room (Finer reference below). For the early CPAP group, one of the criteria that clinicians may use to discontinue CPAP and intubate infants is if their $PaCO_2$ levels exceed 65 mm Hg . Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher $PaCO_2$ levels in premature infants with the primary outcome **being** mortality and/or BPD at 36 weeks and **a secondary outcome of** neurodevelopmental **impairment** at 18-22 months corrected age."

Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL, Kandefer S. Delivery Room Continuous Positive Airway Pressure/Positive End Expiratory Pressure (CPAP/PEEP) In Extremely Low Birth Weight (ELBW) Infants; A Feasibility Trial. Pediatrics 2004 Sep;114(3):651-7.

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, April 19, 2006 3:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

Hi Rose
I like the term "CPAP started in the delivery or following delivery" since previous studies that have used CPAP have used the term early for CPAP started at 4 -12 hours.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 19, 2006 6:12 AM
To: Shankaran, Seetha; Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

It is really "early CPAP" as some children are stabilized in areas adjacent to the DR. –
Neil – your thoughts??
Thanks
Rose

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Wednesday, April 19, 2006 9:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail);

walid.salhab@UTSouthwestern.edu
Subject: RE: Kaiser: Permission to use statement

Rose
Can we state CPAP initiated in the delivery room instead of early?
Thanks
Seetha

Seetha Shankaran, M.D.
Professor of Pediatrics
Wayne State University School of Medicine
Director, Neonatal-Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital

Tel 313-745-1436
Fax 313-745-5867

Email sshankar@med.wayne.edu

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 18, 2006 12:17 PM
To: Neil Finer; alaptook@WIHRI.org; Abhik Das; ambal@uab.edu; aaf2@po.cwru.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Carlo Waldemar (E-mail); Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); Kristi Watterberg; kurt.schibler@cchmc.org; cotte010@mc.duke.edu; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; papile@unm.edu; Poole Kenneth (E-mail); Roger Faix; Ronald GOldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); walid.salhab@UTSouthwestern.edu
Subject: FW: Kaiser: Permission to use statement

Hi,
Dr. Kaiser is requesting permission to use intubation criteria that were developed for the SUPPORT Trial in a chapter that he is currently writing. Please review the language and send me a YES/NO vote by April 21 to allow this use in a published chapter.
FYI – since the protocol is funded by federal dollars, one could go through the FOIA procedure to obtain the protocol as this degree of detail does not appear on the clinicaltrials.gov website. For new centers, usually, in a collaborative spirit, many of these types of requests have been honored by the steering committee.

Please comment on the language:
"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their $PaCO_2$ levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher $PaCO_2$ levels in premature infants with one of the primary outcome **being** mortality and **a secondary outcome of** neurodevelopmental **status** at 18-22 months corrected age."

Thanks
Rose

From: Kaiser, Jeffrey R [mailto:KaiserJeffreyR@uams.edu]
Sent: Tuesday, April 18, 2006 12:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Kaiser: Permission to use statement

Dr. Higgins,
Thanks for speaking to me today regarding a chapter I am writing for a textbook that is being edited by Dr. Michael Schimmel, Director of the NICU at Shaare Zedek Medical Center in Jerusalem. The title of the chapter is Neurological Sequelae Following Mechanical Ventilation, with a proposed subtitle "Neurological Sequelae of Extremes of Carbon Dioxide. I would like to get permission from the NICHD Neonatal Network Steering Committee to use the following sentences:

"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their $PaCO_2$ levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher $PaCO_2$ levels in premature infants with one of the primary outcomes including mortality and neurodevelopmental outcome at 18-22 months corrected age."

I am willing to have the sentences edited as per the Steering Committee.
Thank you for your time,

Jeff Kaiser

Jeffrey R. Kaiser, MD, MA

Associate Professor of Pediatrics and Obstetrics and Gynecology
Section of Neonatology
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University of Arkansas for Medical Sciences
Arkansas Children's Hospital
800 Marshall Street, 512
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tel: (501) 364-1056
beeper: (501) 405(b) (6)
fax: (501) 364-4264
e-mail: kaiserjeffreyr@uams.edu

UAMS office:
tel: (501) 603-1255
fax: (501) 686-8937

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Kaiser: Permission to use statement
Date: Wednesday, April 19, 2006 7:26:10 PM

Hi Rose
The Pilot trial – DR CPAP- used different criteria for intubation, and is already published, and was not powered to look at outcomes. Is Brenda referring to another pilot?
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 19, 2006 10:20 AM
To: Neil Finer
Subject: FW: Kaiser: Permission to use statement

Neil –
Perhaps we should recommend that the main trial was based on the pilot and request inclusion?

Thanks
Rose

From: Brenda Poindexter [mailto:bpoindex@iupui.edu]
Sent: Wednesday, April 19, 2006 12:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Kaiser: Permission to use statement

I would support the request – and also agreed with the changes in wording that Wally suggested. It would be great if he could also reference the pilot trial – at least there is an abstract that could be referenced.
Brenda

Hi,
Dr. Kaiser is requesting permission to use intubation criteria that were developed for the SUPPORT Trial in a chapter that he is currently writing. Please review the language and send me a YES/NO vote by April 21 to allow this use in a published chapter.
FYI – since the protocol is funded by federal dollars, one could go through the FOIA procedure to obtain the protocol as this degree of detail does not appear on the clinicaltrials.gov website. For new centers, usually, in a collaborative spirit, many of these types of requests have been honored by the steering committee.

Please comment on the language:
"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their PaCO2 levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher PaCO2 levels in premature infants with one of the primary outcome **being** mortality and **a secondary outcome of** neurodevelopmental **status** at 18-22 months corrected age."

Thanks
Rose

From: Kaiser, Jeffrey R [mailto:KaiserJeffreyR@uams.edu]
Sent: Tuesday, April 18, 2006 12:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Kaiser: Permission to use statement

Dr. Higgins,
Thanks for speaking to me today regarding a chapter I am writing for a textbook that is being edited by Dr. Michael Schimmel, Director of the NICU at Shaare Zedek Medical Center in Jerusalem. The title of the chapter is Neurological Sequelae Following Mechanical Ventilation, with a proposed subtitle "Neurological Sequelae of Extremes of Carbon Dioxide. I would like to get permission from the NICHD Neonatal Network Steering Committee to use the following sentences:

"Interestingly, the NICHD Neonatal Network is currently performing another important randomized controlled trial comparing the early use of CPAP vs. early intubation and surfactant for premature infants born at 24 to 27 weeks gestation. For the early CPAP group, one of the factors that clinicians may use to discontinue CPAP and intubate infants is if their PaCO2 levels exceed 65 mm Hg. Thus, there will be more information gathered in the setting of a randomized trial regarding the safety of higher PaCO2 levels in premature infants with one of the primary outcomes including mortality and neurodevelopmental outcome at 18-22 months corrected age."

I am willing to have the sentences edited as per the Steering Committee.
Thank you for your time,

Jeff Kaiser

Jeffrey R. Kaiser, MD, MA

Associate Professor of Pediatrics and Obstetrics and Gynecology
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UAMS office:
tel: (501) 603-1255
fax: (501) 686-8937

From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW:
Date: Wednesday, April 19, 2006 6:41:39 PM

OK with me--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 4/19/06 8:33 AM >>>

HI,

I am missing a few votes on this protocol and PhD request. If possible, please send me a response today.

Thanks

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, April 07, 2006 11:21 AM
To: Abbot Laptook (alaptook@WIHRI.org); 'Abhik Das'; Ambal (ambal@uab.edu); Av Fanaroff (aaf2@po.cwru.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Kennedy, Kathleen A; Krisa VanMeurs (VanMeurs, Krisa); 'Kristi Watterberg'; Kurt Schibler (Kurt Schibler [kurt.schibler@cchmc.org]); Michael Cotten (cotte010@mc.duke.edu); 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; papile@unm.edu; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; Walid Salhab (walid.salhab@utsouthwestern.edu)
Cc: 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'
Subject:

Hi,

Attached are a protocol from Jareen Meinzen-Derr at Cincinnati and GDB review from 3/29/2006.

Jareen wants to use this study as part of her PhD. There was extensive discussion about the feasibility of allowing Jareen to go to RTI to access/analyze the data independently, using RTI staff only for support. Drs. Das and Poole have addressed this issue and Ken Poole can serve in a supervisory role-- allowing Jareen to work independently at the same time that they assure that the process of analysis and the outcome/interpretation of the analysis is valid. Jareen will do these

analyses at RTI and data will not be released.

Please send me a YES/NO vote to approve the protocol and allow Jareen to use this for her doctoral dissertation. The publication(s) that result will conform to NRN Policy.

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

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Pablo J. Sanchez, M.D.
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Dallas, TX 75390-9063
214-648-3753
214-648-2481 (fax)

972-206-(b) (6) (beeper)
Pablo.Sanchez@UTSouthwestern.edu

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]; Nancy Miller; Gaynelle Hensley; walid.salhab@UTSouthwestern.edu; Pablo Sanchez; Neil Finer
Cc: Zaterka-Baxter, Kristin; wrich@ucsd.edu
Subject: RE: Stillborn in SUPPORT
Date: Wednesday, April 19, 2006 1:09:35 PM

... and that randomization card should be thrown away and not reused.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, April 19, 2006 1:08 PM
To: Nancy Miller; Gaynelle Hensley; walid.salhab@UTSouthwestern.edu; Pablo Sanchez; Neil Finer
Cc: Das, Abhik; Zaterka-Baxter, Kristin; wrich@ucsd.edu
Subject: FW: Stillborn in SUPPORT

HI,
Even though the card was pulled for randomization, a decision was made not to perform the c-section and subsequently to forgo monitoring of the fetus while in labor. This would meet the exclusion criteria of "decision to forgo full resuscitation."
No SUPPORT or GDB Trial forms should be filled out. However, if there is approval of the antenatal consent protocol, the forms for this study should be filled out.

Thanks
Rose
-----Original Message-----
From: Nancy Miller [mailto:Nancy.Miller@UTSouthwestern.edu]
Sent: Wednesday, April 19, 2006 11:29 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gaynelle Hensley; Pablo Sanchez; Walid Salhab
Subject: RE: Stillborn in SUPPORT

Rose,
Dr Salhab discussed the case with the Fellow present at the delivery and with the OB Attending. Here's all of the information I have on the circumstances surrounding this birth. The Mom was consented for SUPPORT on (b) (6) and turned 24 0/7 wks on (b) (6) A STAT C/S was called on (b) (6) for this Mom due to a prolapsed cord. The baby was not having bradycardia or De sats. The Resus team went to the delivery thinking there was going to be a STAT C/S and opened the randomization card. In the OR the OB talked to the parents and discussed the prognosis of the infant. Following that they agreed not to proceed with the C/S. They induced the Mom to deliver vaginally. The Infant was not monitored during the induction.
We don't know when the baby died or became bradycardic. The infant was stillborn at birth.
Hope this helps.
Thanks,
Nancy

Nancy A. Miller, R.N.
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd. E3-502
Dallas, Texas 75390-9063
214-648-3780
pager 972-206-(b) (6)

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT oximeters & time change
Date: Tuesday, April 18, 2006 4:24:31 PM

Should I send this to the collaborating sites. Do they still have kids on the massimos and if not, since it may be a bit before they ship the massimos to the new sites (depends on the new sites IRB approvals), should we ask them to adjust the time on their respective oximeters if they've not already do so prior to shipping?
Thanks
Kris

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, April 18, 2006 2:29 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Neil Finer
Cc: Zaterka-Baxter, Kristin; Schaefer, Scott E.
Subject: FW: SUPPORT oximeters & time change

Kris,
Here is what we sent out last time. Since it is already past, the part about Monday is no longer relevant. It should say:

1) Please change all oximeters not currently in use to back to Standard time if you switched them to Daylight Savings time last fall.
2) Do not change any oximeters which are in use until the subject has completed his data set (36 weeks or off of oxygen x 3 days.)

wade

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, October 26, 2005 3:05 PM
To: 'Hastings, Betty J.'
Subject: FW: SUPPORT oximeters & time change

Daylite savings time changes for Support:

1) Change all oximeters not in current use on Monday.
2) Do not change oximeters currently in use until they are put on another patient. RTI will make any necessary back-corrections at their end.

Wade

From: Pickett, James [mailto:japickett@rti.org]
Sent: Wednesday, October 26, 2005 2:51 PM
To: wrich@ucsd.edu; Schaefer, Scott E.
Cc: Gantz, Marie
Subject: RE: SUPPORT oximeters & time change

Yes, and change the meters that were in current use before they are used on another patient.

J

James Pickett - Programmer / Analyst
(919) 541-1253 * 4E13A 800 Park * japickett@rti.org
RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research Triangle Park, NC 27709-2194

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, October 26, 2005 5:48 PM
To: Pickett, James; Schaefer, Scott E.
Cc: Gantz, Marie
Subject: RE: SUPPORT oximeters & time change

Translation: Change oximeters not in current use. Do not change oximeters in current use. Correct?
wade

From: Pickett, James [mailto:japickett@rti.org]
Sent: Wednesday, October 26, 2005 2:39 PM
To: Schaefer, Scott E.; wrich@ucsd.edu
Cc: Gantz, Marie
Subject: RE: SUPPORT oximeters & time change

I would suggest changing the time on out of use meters right away, but NOT changing the time on in use meters until the child is taken off for good. Then you will have a continuous and relevant stream of data (which is what you should care about more than the date) to analyze. Plus with this method you can take account for DST on the back end (if date is an extremely important data point) by saying people with readings that started before DST didn't fall back and should be adjusted accordingly. People that started on meters after DST will have correct dates and don't have to be bothered.

J

James Pickett - Programmer / Analyst
(919) 541-1253 * 4E13A 800 Park * japickett@rti.org
RTI International * 3040 Cornwallis Road * P.O. Box 12194 * Research Triangle Park, NC 27709-2194

From: Schaefer, Scott E.
Sent: Wednesday, October 26, 2005 5:24 PM
To: 'wrich@ucsd.edu'
Cc: Gantz, Marie; Pickett, James; Schaefer, Scott E.
Subject: RE: SUPPORT oximeters & time change

If They take the child off of the meter to download and reset the clock for daylight savings time, AND take less than an hour to start the child again, the data within that hour will be ignored in the analysis. On the other hand, if everybody doesn't change the time, then an hour each day will be assigned to the wrong date.

What to do...

Scott *8-)

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Wednesday, October 26, 2005 4:10 PM
To: Schaefer, Scott E.
Subject: FW: SUPPORT oximeters & time change

Scott,
An hour of data will show up twice if we do this. Will you be able to handle that?
wade

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, October 26, 2005 12:43 PM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: Hastings, Betty J.; higginsr@mail.nih.gov; Das, Abhik; Auman, Jeanette O.; Poole, W. Kenneth; Zaterka-Baxter, Kristin; Gantz, Marie; Schaefer, Scott E.; 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; mcollins@peds.uab.edu; monica.konstantino@yale.edu; Nancy.Miller@utsouthwestern.edu; ae5357@wayne.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; Nancy Newman
Subject: SUPPORT oximeters & time change

Wade,

At Wake Forest we will go on "Daylight Savings Time" this weekend. I know that this change may not affect all centers, but how will this affect the SUPPORT Trial study oximeters and analysis of the downloaded information and correlation to data that might be collected on data forms? Do we do a download from all study oximeters on Monday morning and change the time then or just change the time when we do the next scheduled download?

Thanks. (not something I can take the credit for thinking of....a question from one of our research staff, and I did not know the answer)

Nancy P.

From: Nancy Newman
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE:
Date: Tuesday, April 18, 2006 1:04:01 PM

Hi- I do not need oximeters now just wanted you to know our status. Also- I'll FedEx the 1572 and CV to arrive tomorrow.....NN

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, April 18, 2006 11:10 AM
To: Nancy Newman
Subject: RE:

Please mail me the 1572 and the CV. Also, let me know what color oximeters you will need and I will ask Wade to send them to you.
The trip was great!!
Thanks
Rose

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, April 18, 2006 10:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject:

Hi Rose- I am faxing the 1572 now for the Inositol pilot- what about the PI's CV??

Also, we presently have 10 infants randomized in SUPPORT since re-starting. So I have 10 oximeters in use plus we still have consents pending requiring 2 of each color available. AND one oximeter was returned to Masimo for repair- it was giving us a code of 007- what ever that means! And another which I need to call Masimo about today- we cannot seem to clear the data after the download. So- just wanted you to know where we stand as far as available equipment- we have 2 available- I need to check for colors.

I will be on the SUPPORT call tomorrow for the new centers- But Thursday I was planning to take the day off- so I'll miss the coordinator call. Sorry.

Hope your trip was great.....NN

From:	Neil Finer
To:	Phelps, Dale; Jensen, Rosemary; Reubens, Linda; Stevens, Timothy
Cc:	Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Wade Rich
Subject:	RE: SUPPORT withdrawal infant, but can baby be in Breathing Study
Date:	Monday, April 17, 2006 1:27:15 PM

Hi Dale and Rosie
I agree that it would be appropriate to discuss with the parents. If they are agreeable to allow the infant's data to be used, then this should be documented, and they could be approached about the Breathing Outcomes study, and the MRI study.
I would also inform your IRB about the withdrawal and subsequent decisions to use the infant's data.
As the withdrawal of the oximeter was on parental request, I would so indicate and this should not be a protocol violation, but rather a withdrawal from the study.
Were you able to get permission to download the oximeter?
Let me know how this plays out.
Neil

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, April 17, 2006 6:11 AM
To: Jensen, Rosemary; Reubens, Linda; Stevens, Timothy
Cc: Zaterka-Baxter, Kristin; Neil Finer; Rosemary Higgins
Subject: SUPPORT withdrawal infant, but can baby be in Breathing Study

Hi Rosie,
This is an interesting question with several twists.

Consented to SUPPORT.
Over 1kg

Withdrew from support after _____ days of age (close to the end of the oximeter time).

GDB data will be in the database.
Early SUPPORT data will be in the database, but the late SUPPORT data (rest of hospitalization) will not.
Would not be seen at 18 months if completed withdrawn from study.

If parents consent to breathing study, would need to collect:
rest of data forms from SUPPORT.
the Breathing study forms, interviews and follow up.
Schedule into 18 month follow up

So what you and Tim would need to negotiate is agreement from the family that while they withdrew from the oximeter intervention portion of the study, they are willing to continue with the follow up part. If they agree, we would need a clear note in their file (attach to consent), and I think the early stopping of the oximeter would then be a kind of protocol violation. -- Kris could tell us what form to complete if the re-recruitment was successful.

I am going to copy Kris and Neil on this one for their comments and thoughts.

Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester School of Medicine and Dentistry
Division of Neonatology, Pediatrics, Box 651

601 Elmwood Ave
Rochester, NY 14642

(585) 275-2972
FAX (585) 461-3614

From:	Zaterka-Baxter, Kristin
To:	Phelps, Dale; Stevens, Timothy
Cc:	Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; Gantz, Marie
Subject:	RE: SUPPORT withdrawal infant, but can baby be in Breathing Study
Date:	Monday, April 17, 2006 1:23:50 PM

Hi,
From the DCC perspective, this may not be a protocol violation if the patient was withdrawn by the parents from study. Once withdrawn from study, no further 'Support' data should be collected though this may be up to their local IRB. If the parents do consent to the support Follow up and BO, data may then be able to be collected (if in GDB, we would probably have status data regardless). There doesn't appear to be a clear cut question in the support forms that would allow you to document withdrawn from study. Ken and Abhik agree we need to know consent was withdrawn and have suggested possibly leaving the status as missing and entering a comment of "withdrawn" or we can add a code for withdrawn to the SUPP09 form.

Thanks,
Kris

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, April 17, 2006 9:11 AM
To: Jensen, Rosemary; Reubens, Linda; Stevens, Timothy
Cc: Zaterka-Baxter, Kristin; Neil Finer; Rosemary Higgins
Subject: SUPPORT withdrawal infant, but can baby be in Breathing Study

Hi Rosie,
This is an interesting question with several twists.

Consented to SUPPORT.
Over 1kg

Withdrew from support after _____ days of age (close to the end of the oximeter time).

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rest of data forms from SUPPORT.
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So what you and Tim would need to negotiate is agreement from the family that while they withdrew from the oximeter intervention portion of the study, they are willing to continue with the follow up part. If they agree, we would need a clear note in their file (attach to consent), and I think the early stopping of the oximeter would then be a kind of protocol violation. -- Kris could tell us what form to complete if the re-recruitment was successful.

I am going to copy Kris and Neil on this one for their comments and thoughts.

Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology

University of Rochester School of Medicine and Dentistry
Division of Neonatology, Pediatrics, Box 651
601 Elmwood Ave
Rochester, NY 14642

(585) 275-2972
FAX (585) 461-3614

From: Wade Rich
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; ellen.hale@oz.ped.emory.edu
Subject: RE: SUPPORT - Vapotherm
Date: Monday, April 17, 2006 12:34:13 PM

And the answer to Ellen's question is yes, the use of high flow cannula is not allowed in the first 14 days of the trial, no matter whose name is on the box. The intent is that if you are going to use CPAP that it be pressure driven, monitored, alarm protected CPAP, not unregulated flow.
Wade

From: Neil Finer
Sent: Monday, April 17, 2006 9:30 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; ellen.hale@oz.ped.emory.edu
Cc: Wade Rich
Subject: RE: SUPPORT - Vapotherm

Hello Rose

The vapotherm was removed form the market secondary to concerns about infection. I have copied the relevant material below.

Hope this helps

Neil

Vapotherm 2000i Respiratory Gas Administration Device

Audience: Neonatologists, Respiratory healthcare professionals and hospital clinical managers

[UPDATE posted 12/20/2005] See update of safety information about *Ralstonia* spp. associated with Vapotherm Respiratory Gas Administration Device. The FDA continues to collaborate with the CDC to determine the scope of the contamination with *Ralstonia spp.*, and other opportunistic pathogens. Further information is proved in the updated MMWR from CDC.

[Posted 10/27/2005] FDA issued a Preliminary Public Health Notification to inform healthcare professionals of new information about a possible association between the Vapotherm 2000i Respiratory Gas Administration device, used to add moisture and warm breathing gases through a nasal canula in patients receiving supplemental oxygen, and the occurrence of positive Ralstonia spp. cultures. The association was first reported in a MMWR article issued by CDC on October 21, 2005. The new information is described in the web notice at the link below. FDA recommends that providers consider this new information in deciding whether and when to use the Vapotherm device with patients.

[December 20, 2005 - Update: Preliminary Public Health Notification - FDA]

[December 20, 2005 - Morbidity and Mortality Weekly Report - CDC]
[October 27, 2005 - Preliminary Public Health Notification - FDA]
[October 19, 2005 - Morbidity and Mortality Weekly Report - CDC]

Vapotherm 2000i Respiratory Gas Administration Device

Audience: Neonatologists, Respiratory healthcare professionals and hospital clinical managers

[UPDATE posted 12/20/2005] See update of safety information about *Ralstonia* spp. associated with Vapotherm Respiratory Gas Administration Device. The FDA continues to collaborate with the CDC to determine the scope of the contamination with *Ralstonia spp.*, and other opportunistic pathogens. Further information is proved in the updated MMWR from CDC.

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[December 20, 2005 - Update: Preliminary Public Health Notification - FDA]
[December 20, 2005 - Morbidity and Mortality Weekly Report - CDC]
[October 27, 2005 - Preliminary Public Health Notification - FDA]
[October 19, 2005 - Morbidity and Mortality Weekly Report - CDC]

The device was pulled as noted below:

FDA Warns Against Use of Vapotherm Device

Yael Waknine

Dec. 21, 2005 — In an update to a preliminary public health notification issued October 27, the U.S. Food and Drug Administration (FDA) advised healthcare professionals to cease using a respiratory gas administration device (Vapotherm 2000i, made by Vapotherm, Inc), due to the risk for patient exposure to *Ralstonia* species.

The association was first reported by the Centers for Disease Control and Prevention (CDC) in the Oct. 21 issue of the *Morbidity and Mortality Weekly Report*, and involved the recovery of *Ralstonia spp.* from clinical specimens and/or respiratory devices in a number of healthcare facilities.

In response, the company developed new infection-control guidelines that included a chlorine dioxide protocol to disinfect the device and associated cartridges. Data reported by the FDA in the Oct. 27

notification questioned the protocol's efficacy in achieving bacterial control.

Since then, the FDA has become aware of additional *Ralstonia spp.* cultures from these devices and from exposed patients, according to an alert sent yesterday from MedWatch, the FDA's safety information and adverse event reporting system. Overall, the bacteria have been recovered in 29 institutions across 16 states, and from approximately 40 pediatric patients.

Moreover, *Ralstonia spp.* has been cultured from systems disinfected according to the new protocol as well as initial company instructions. Cultures of unused cartridges also yielded *Ralstonia spp.* at 2 hospitals, although similar analyses of other unused cartridges from the same lot did not reveal any organisms.

Until the source of contamination has been identified, an alternative breathing device should be used. A list of options is available online at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm, and may be searched using "BTT" in the product code field.

The FDA notes that several of the humidifiers on the list for use with infant or adult ventilators have specifications similar to that of the Vapotherm device and use heated outlet tubes. The humidifiers will require a gas source, connectors, and a patient mask or cannula to form a complete system for breathing gas administration.

Patients exposed to the breathing device should be monitored for signs and symptoms of infection such as changes in temperature, poor feeding, irritability, and changes in hematologic indices. Clinicians may wish to consider *Ralstonia spp.* in the differential diagnosis even if it has not been isolated.

According to the FDA, additional testing is currently being conducted to determine the source and scope of *Ralstonia spp.* contamination and evaluate new disinfection protocols. Further updates will be provided as new information becomes available.

Clinicians are encouraged to report cases of *Ralstonia spp.* in patients using any Vapotherm 2000 respiratory gas administration device. This information may be communicated directly to the device manufacturer, local or state health departments, or to the CDC at 1-800-893-0485.

These cases and any other adverse events related to the device should also be reported to the FDA's MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, online at http://www.accessdata.fda.gov/scripts/medwatch/, or by mail to 5600 Fishers Lane, Rockville, MD 20852-9787.

More information regarding possible *Ralstonia spp.* contamination of the respiratory therapy devices may be obtained by contacting the Office of Surveillance and Biometrics (HFZ-510) by mail at 1350 Piccard Drive, Rockville, MD, 20850, by fax at 301-594-2968, by email to phann@cdrh.fda.gov, or by leaving a voice mail message at 301-594-0650.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 17, 2006 9:03 AM
To: Neil Finer; Wade Rich
Subject: FW: SUPPORT

Can you help out with this question? Was vapotherm removed from the market???
Thanks

Rose

From: Ellen Hale [mailto:ellen.hale@oz.ped.emory.edu]
Sent: Thursday, April 13, 2006 2:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kzaterka@rti.org
Subject: SUPPORT

Dear Rose,

Are we correct in that no high flow (> 1 liter per minute nasal cannula) is to be used for SUPPORT patients in the first 14 days? Now that vapotherm has been taken off the market there are other mechanisms out there to deliver high flow. I found this to be true this morning when I found our SUPPORT patient using one. Maybe others need to be aware of this problem.

Ellen

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT consent
Date: Thursday, April 06, 2006 11:21:28 AM
Attachments: Fianl UnstampedCONSENT 090104.DOC

UCSD Main Support trial consent. They do use three separate consents.

Thanks,
Kris

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, April 06, 2006 11:13 AM
To: Zaterka-Baxter, Kristin
Subject: RE: SUPPORT consent

Correct. And since you are planning to ask, attached is my support consent.
wade

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, April 06, 2006 8:08 AM
To: wrich@ucsd.edu
Subject: RE: SUPPORT consent

Thanks for sending these. You guys have three consents right (main, MRI, BO)?

Thanks,
Kris

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, April 06, 2006 10:43 AM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT consent

Kris,
Attached are our approved consents for the breathing outcomes and
MRI.

Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 06, 2006 7:31 AM
To: wrich@ucsd.edu; nfiner@ucsd.edu
Cc: kzaterka@rti.org
Subject: Re: SUPPORT consent

The new sites would like to see tham. Can you send the approved

documents
in word to Kris or myself to send to the new sites?
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>;
nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Thu Apr 06 09:45:30 2006
Subject: RE: SUPPORT consent

We did not. Our only pulmonary outcome request was for kids already
enrolled, because we knew we would not be able to enroll by the time we
were
able to get the protocol approved. MRI was a stand alone because it was
so
easy to get, and we did not want to further complicate the main study
consent.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, April 06, 2006 5:16 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Subject: SUPPORT consent

Hi Neil and Wade,
The new sites were asking about rolling mri and pulmonary outcomes into
the
main support trial consent. I believe you may have done this - if so,
please send us an electronic versioon of the approved consent. We think
this may help speed the process (especially if we can say other irbs
approved it this way).

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

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)
And,
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 the 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.

_____	_____	_____
Subject's signature	Witness	Date

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Tuesday, April 04, 2006 3:55:49 PM

No this was in 1996

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) [E]
Sent: Tuesday, April 04, 2006 3:53 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: Re: SUPPORT

Is this why (b) (5) ?

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E] <spongc@dir49.nichd.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Tue Apr 04 15:47:58 2006
Subject: RE: SUPPORT

Yes (b) (5)

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) [E]
Sent: Tuesday, April 04, 2006 3:47 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: Re: SUPPORT

Duke wanted to add (b) (5) and I had already sent duke the checklist that is used to add a second site.

I agree that it is (b) (5) .
(b) (5) ??

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E] <spongc@dir49.nichd.nih.gov>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Tue Apr 04 15:44:12 2006
Subject: RE: SUPPORT

Yikes that is (b) (5) [redacted]
YUCK

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) [E]
Sent: Tuesday, April 04, 2006 3:40 PM
To: Spong, Catherine (NIH/NICHD) [E]
Subject: SUPPORT

Cathy
Yale (Rich ehrenkranz) wants to add (b) (5) [redacted] - how shall I answer this. I told Richard that I needed to check!!
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Tuesday, April 04, 2006 3:16:44 PM

Yes

Sent from my BlackBerry Wireless Handheld

----- Original Message -----
From: "Higgins, Rosemary \(NIH/NICHD\) [E]" [higginsr@mail.nih.gov]
Sent: 04/04/2006 03:09 PM
To: <goldb008@mc.duke.edu>
Subject: SUPPORT

I need a yes/no vote for neil remaining pi for support.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Monday, April 03, 2006 11:17:53 PM

Hi Rose
I doubt that we would bother her - apart from having the most current enrollments including the MRI and Pulmonary Follow.
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, April 03, 2006 12:07 PM
To: nfiner@ucsd.edu
Subject: SUPPORT

Neil
Abhik has suggested that Marie be available for the 1 hour subcommittee meeting tomorrow just in case we need her. We are in the process of checking with her and setting up the phone in the room. Let me know if you think of anything else that we may need. I will have email access or you can call.
(Home 703-827(b) (6)if needed).

See you tomorrow

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: draft email for SUPPORT sites
Date: Monday, March 27, 2006 12:14:55 PM

Hi Rose

Below is the draft of the email I would like to send to alert sites to the possibility of using the MedVac System. I have a disclaimer for the NIH and NICHD in paragraph 3.

Let me know if it's OK to send - I suppose I should send it because then it doesn't look too official?

Susan

****

March 27, 2006

Subject: Infant Immobilizer (MedVac System) for obtaining MRI's

From: Susan Hintz, M.D.

Most of the Neonatal Research Network sites participating in the SUPPORT Neuroimaging secondary plan to obtain near-term brain MRI's without sedation. The Stanford site has been routinely obtaining MRI's without sedation for the past few years using the "feed and swaddle with a blanket" method. However, many researchers in Australia, New Zealand, and Europe have used inflatable immobilizers with excellent success. As many of you know, Wade Rich and Neil Finer at UCSD have started using such a device, called the MedVac Infant Immobilizer. The UCSD site had not previously performed neonatal brain MRI's without sedation, and they have had outstanding results with this device.

I have talked quite a bit with the distributors of the MedVac Immobilizer (Contour Fabricators, Inc. Medical Solutions

(CFI)), and they would be very happy to help any of the Network sites with getting a device on "consignment" - that is, the site would get a device to try out for a period of time free of charge, with the option to purchase. The distributors have also been very responsive in terms of coming to sites to demonstrate the system. The device is fairly simple, and consists of an inflatable hugging blanket and manual air pump.

The NIH and NICHD cannot officially "endorse" or "not endorse" this or any product for this study or any purpose. But, it is an option available to institutions that may help some in not only obtaining research-related MRI's, but also be utilized for clinical purposes.

If you are interested, please contact the "point people" for CFI directly (see below). They will help you directly, or put you in touch with someone closer to your site:

John Lochner
Marketing and Sales Coordinator of CFI Medical Solutions
Email: john.lochner@contourfab.com
Phone: 810-750-5300, ext 215

Greg Weaver
West Coast Sales Representative
Email: weaver.g@comcast.net
Phone: 323-653-2805

From: Susan Hintz
To: kristin zaterka
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: emails for various sites re SUPPORT secondary
Date: Thursday, March 23, 2006 4:07:52 PM
Attachments: emails032306.doc

Kristin,

Below are FOUR emails that I would like to send to the sites indicated to get a bit more information about SUPPORT Neuroimaging secondary participation. I have spoken to Rose about this, and she has OK'd the emails going out. Please just copy me on the emails - I understand that you will need to "blind" the new site emails to me.

Also, you will probably see that most of the questions are consistent with the excel spreadsheet you have sent me. However, could you please just add two new columns: 1) have MRIs or CUS been sent to RTI by the site, and 2) main limitations to participation.

Thanks so much Kristin. Let me know if any of this doesn't make sense.

Susan Hintz

--

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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Thanks so much Kristin. Let me know if any of this doesn't make sense.

Susan Hintz

FOR sites who have not responded (i.e., Wayne, Cincinnati, Emory, Yale):

With the reactivation of SUPPORT enrollment in February and the Steering Committee meeting approaching, we would like information about participation in the SUPPORT Neuroimaging secondary to be as complete as possible. We have not yet heard definitively from your site about whether you are planning to participate in this secondary.

Please respond to the following:

1. Has your site received IRB approval for the SUPPORT Neuroimaging secondary?

If yes, what was the approval date?

2. If your site has received IRB approval or approval is pending, will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall study consent?

3. If your site has not received IRB approval, has your site applied for IRB approval for the SUPPORT Neuroimaging secondary?

If not, does your site intend to participate?

4. If your site does not intend to participate, what were the main limitations for participation?

FOR sites with IRB approval "pending" (Case, Indiana, Duke):

With the reactivation of SUPPORT enrollment in February and the Steering Committee meeting approaching, we would like information about participation in the SUPPORT Neuroimaging secondary to be as complete as possible. Our last update from your center was that IRB approval for the SUPPORT Neuroimaging secondary was "pending".

Please respond to the following:

Has your site received IRB approval for the SUPPORT Neuroimaging secondary?

If yes, what was the approval date?

If IRB approval has been granted, has your site performed any study-related brain MRI's or cranial US yet?

For sites with IRB approval (Alabama, Dallas, Brown, Stanford, Houston):

With the reactivation of SUPPORT enrollment in February, we would like to make sure that the SUPPORT Neuroimaging secondary is also on track. Previously, your site has indicated that IRB approval has already been granted for the SUPPORT Neuroimaging secondary.

Please respond to the question below:

Has your site performed any study-related MRI's or cranial US yet?

Also, as a reminder, we are asking that study-related MRI's and cranial US be sent to RTI *routinely* – the manual indicates that neuroimaging CD's should be sent to RTI *monthly*, although this may not be necessary for all sites depending on the volume of enrollment. The reason we have requested that neuroimaging be sent routinely is two-fold: 1) it is likely to be easier for sites to obtain CD

duplicates of studies in "near real-time" rather than at the end of the trial, and 2) this procedure will facilitate "rolling" central reading, particularly of the MRI's.

Below is the section of the manual pertaining to preparing and sending neuroimaging studies. PLEASE NOTE THAT THE MANUAL HAS BEEN UPDATED TO REFLECT THAT KRISTIN ZATERKA-BAXTER will be receiving the studies for RTI.

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 (Digital Imaging and Communications in Medicine) 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.*

Removing PHI from digitized images may be difficult for some centers. Radiology departments at most centers can create duplicate "anonymous exams" on their systems; these "anonymous exams" may then be copied to CD. This procedure, which removes PHI from the image headers, has been particularly useful in previous MRI-related research. Radiology departments at other centers may use software that allows for alteration or "blacking out" of PHI headers after images are transferred to CD. However, if these options are not available at your center, additional language could be added to the secondary consent form explaining that central readers will interpret the images, which include headers, but will not have other information about the patient. Each center will need to work with their individual Radiology departments, and follow the requirements of their IRB with respect to the consent process.

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.

Kristin Zaterka-Baxter
4426 South Miami Blvd.
Durham, NC 27703
919-485-7750

FOR new Network sites:

With the reactivation of SUPPORT enrollment in February and the Steering Committee meeting approaching, we would like information about participation in the SUPPORT Neuroimaging secondary to be as complete as possible. As a new participating site in the Neonatal Research Network, we would like to know your plans about participation in the SUPPORT Neuroimaging secondary.

Please respond to the following:

1. Is IRB approval pending for the SUPPORT Neuroimaging secondary at your site?

If yes, will your site be using a separate consent for the Neuroimaging secondary, or will the consent be embedded in the overall SUPPORT consent?

2. If IRB approval is not pending at your site, does your site intend to participate in the SUPPORT Neuroimaging secondary?

3. If your site does not intend to participate, what were the main limitations for participation?

From:	Neil Finer
To:	"Lisa Askie"; williamt@westgate.wh.usyd.edu.au; schmidt@mcmaster.ca; bdarlow@chmeds.ac.nz; ccole@bidmc.harvard.edu; shey@easynet.co.uk; John@ctc.usyd.edu.au
Cc:	"Jenny Chow"; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: NeOProM prospective meta-analysis protocol
Date:	Thursday, March 23, 2006 1:20:19 PM

Hi Lisa
We have looked at the protocol with respect to the data that is being collected for SUPPORT
Page 12 #8 - Steroids for Chronic Lung Disease is not delineated in Support, and is only recorded as the receipt of steroids after 14 days. The GDB of the Network does ask the question as to whether the infant received steroids for CLD, irrespective of the infant's age
#11 - We do not define transport to non-tertiary centers specifically in SUPPORT or the GDB.
Page 13 #2 Bailey III will be used for SUPPORT.
I will look forward to the conference call.
Neil Finer

From: Lisa Askie [mailto:laskie@ctc.usyd.edu.au]
Sent: Tuesday, March 21, 2006 8:22 PM
To: williamt@westgate.wh.usyd.edu.au; schmidt@mcmaster.ca; bdarlow@chmeds.ac.nz; ccole@bidmc.harvard.edu; shey@easynet.co.uk; John@ctc.usyd.edu.au; nfiner@ucsd.edu
Cc: Jenny Chow
Subject: NeOProM prospective meta-analysis protocol

Neil, William, Brian, Edmund, Barbara, Cynthia and John,

Please find attached the **revised version of the draft protocol for the planned prospective meta-analysis of neonatal oxygen trials for your review.**

As indicated previously, I would suggest the following:
1. All PIs review the draft protocol and **please reply with comments / suggested amendments.**
2. We discuss the revised protocol and other management issues (see below) by teleconference in about two weeks time.
3. Those going to SPR in San Francisco (+ other interested people) meet whilst there.

Potential items for discussion at the teleconf and/or SPR meeting:
1. Common, core data items - what to collect, definitions (starting point could be to read attached BOOST 2 Aus data fields)
2. Interaction between DSMC for each trial (see proposal on page 15 of draft protocol)
3. Decision re Collaboration's official name
4. Management plan and structure (see relevant sections in draft protocol)
5. Funding plans

Our Executive Officer, Jenny Chow, will be in touch shortly regarding everyone's **availability for a teleconference in the week 3-7 April.**

Cynthia is organising a date / time / venue for the SPR meeting and once this is confirmed I will circulate the proposed agenda and accompanying papers.

Looking forward to kick starting our prospective meta-analysis Collaboration officially at last!

Regards,
Lisa

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Dr Lisa Askie PhD MPH

Research Fellow, School of Public Health
Manager, Australian Clinical Trials Registry

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University of Sydney
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Camperdown. NSW. 2050.
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Tel: +61 (0)2 9562 5000
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Fax: +61 (0)2 9565 1863
Mobile:+61 (0)4 2333(b) (6)
Email: laskie@ctc.usyd.edu.au
Web: www.ctc.usyd.edu.au
<><><><><><><><><><><><><><><><><><><><>

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: New sites/oximter transfer
Date: Wednesday, March 22, 2006 8:58:39 AM

I can wait on this part if you want me to. Everything thing else is ready.
Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, March 22, 2006 8:57 AM
To: Hastings, Betty J.
Cc: Das, Abhik
Subject: RE: New sites/oximter transfer

This is fine. I have only formally discussed this with Mike O'Shea so far, but will talk to the other PI's. Neil's site has been a storing house anyway, so he should be OK with it. None of the sites have gone to the IRB with the protocol thus far.

Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Wednesday, March 22, 2006 8:51 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: New sites/oximter transfer

Rose,
I'm working on the SUPPORT randomizations for the new centers and wanted to make sure if the following oximeters will definitely be shipped from the old sites to the new ones listed before I get too far along on this.

Oximeters shipped from Wake Forest to Tufts University (Center 23))
Oximeters shipped from Rochester to University of Iowa (Center 24)
Oximeters shipped from UCSD to University of Utah (Center 25)
Oximeters shipped from Miami to University of New Mexico (Center 26)

Thanks a lot for your help.
Betty

From: Nancy Newman
To: wrich@ucsd.edu; "Zaterka-Baxter, Kristin"
Cc: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; ahensman@wihri.org
Subject: RE: Support Form 5 and 5a clarifications
Date: Tuesday, March 21, 2006 3:12:34 PM

Hi- I understand how the form works- but the question that I understand was raised was that if a blood gas is from days before when an infant is stable and then he/she may crash and be intubated with no blood gas done- even if you say yes to other parameters- was good is a 'good or stable' blood gas that is not at all reflecting the status of the infant at the time a gas is done? And some of the coordinators seem to want to document a gas that may be far out.....NN

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, March 21, 2006 2:37 PM
To: 'Nancy Newman'; 'Zaterka-Baxter, Kristin'
Cc: nfiner@ucsd.edu; 'Rosemary (NIH/NICHD) [E] Higgins'; ahensman@wihri.org
Subject: RE: Support Form 5 and 5a clarifications

Nancy,

We agree with you, but this is basically a piece of data which can not be verified. We do not include a date/time for the blood gas data related to intubation or extubation. The idea behind it was that if none of the other boxes were checked, this blood gas data would show the reason why you intubated/extubated. It is assumed that no one will make
a decision to intubate for a CO2 of 75 that is 48 hours old. But if they do, you still want to know that they intubated for a CO2 of 75, not for apnea.
Wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Tuesday, March 21, 2006 11:22 AM
To: 'Zaterka-Baxter, Kristin'
Cc: nfiner@ucsd.edu; 'Rosemary (NIH/NICHD) [E] Higgins'; wrich@ucsd.edu; ahensman@wihri.org
Subject: RE: Support Form 5 and 5a clarifications

Kris- I see your request for clarification and what you wrote for question #2 is good – as we worked on last week- but to me I think that for the intubation/extubation information – the blood gas should reflect that the infant is deteriorating and needs intubation OR that the infant has done well and is being extubated- and if there is no blood gas near (???time) the int/extubation then it should be **** to indicate not done. Let Neil decide what the reasonable time frame should be- but probably not days or a week from the int/extubation.....NN

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, March 21, 2006 12:31 PM
To: nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Nancy Newman; ahensman@wihri.org; Ellen Hale; Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Support Form 5 and 5a clarifications

Hi,
We would like to send out a technical memo this week clarifying Appendix F (management of 02 conc.) and the two questions below. If either of you have a moment to answer these questions, it would be greatly appreciated.

Thanks so much,

Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Wednesday, March 15, 2006 10:31 AM
To: 'nfiner@ucsd.edu'
Cc: 'Nancy Newman'; 'Ellen Hale'; 'Wade Rich (wrich@ucsd.edu)'; 'Angelita Hensman (ahensman@wihri.org)'; Hastings, Betty J.
Subject: Support Form 5 and 5a clarifications

Hi Dr. Finer,
In attempting to utilize the support forms that were recently revised, two questions have come up for which we would very much appreciate your in put:

1. Form Supp05a; is there a time limit for the collection of ABG data prior to intubation/extubation (i.e., 24 hrs verses 7 days or longer prior to the event) forms attached with the section in question highlighted. Please note we would like to clarify this in the MOP only.

2. Form Supp05; when recording the ABG values in the given slot on the data form, the recording method now indicates two FiO2 measurements to be recorded in one slot (i.e., if a gas was drawn at 0600, it is recorded in the given 0800 time slot (to include FiO2) however at 0800, an FiO2 measurement is also to be recorded (the q2hr measurements). It has been suggested that the FiO2 measurement corresponding to the gas supersedes the q2hr FiO2 measurements for this time period. (see highlighted form section attached and suggested revised text for the MOP)

Regarding question 2: please see below for suggested MOP clarifications (in blue):

10.2.1 Section A. Blood gas results, FiO_2 and Mode of Support closest to the scheduled times will be recorded. **Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59.** If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support. **In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.**

Note that the FiO2 corresponding with the ABG analyses will be recorded in the given time slot (08:00, 16:00, and 23:59) and will supersede the FiO2 measurements obtained q2hrs.

Please let me know your thoughts and we can add any revisions to the technical memo we will be sending out to clarify Appendix F.
Thanks for your time,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703

Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: How is SUPPORT Going ?
Date: Monday, March 20, 2006 1:30:14 PM

Hi Rose
I have no idea.
I didn't feel the need to divulge this information. Is this information privileged?
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 20, 2006 7:33 AM
To: nfiner@ucsd.edu
Subject: RE: How is SUPPORT Going ?

Neil
Is there some reason Dr. Hey wants to know the membership of the DSMC??
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, March 20, 2006 10:14 AM
To: 'Edmund Hey'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: How is SUPPORT Going ?

Hi Edmund
We are continuing to recruit and will hopefully reach full enrollment barring any safety issues.
We are going to the Bayley III
We are starting site visits and there is no one person who is charged with the accuracy and thus we will be doing compliance visits to ensure that the information is accurate.
I will copy Rose Higgins with this email. I do know the members of the committee but I am uncertain if I can share this so I will ask her to respond on this issue.
Congratulations on getting your study funded. I will be in England in November at the NEONATAL UPDATE 2006, , 27 November - 1 December 2006 at The Wolfson Conference Centre, Imperial College London.
Perhaps we can meet and discuss any issues you may have at that time.
Be well
Neil

From: Edmund Hey [mailto:(b) (6)
Sent: Monday, March 20, 2006 6:33 AM
To: Finer, Neil
Subject: How is SUPPORT Going ?

Neil,

We have a major management meeting here in three days time to start working on the details of the version of BOOST-II that has now been funded in the UK. Can I tell them that recruitment for SUPPORT is now running smoothly again ? Do you plan to go on recruiting until you have 1320 babies in the bag or does the guillotine come down on recruitment at some fixed date irrespective of how recruitment is then

going ?

I am sure I asked you this once before but I need to ask you again because all my old e-mail messages got wiped off my machine six months ago. Are you going to be using Bayley II or Bayley III to assess neurodevelopmental impairment ? It must be in your protocol somewhere, but I could not find it quickly.

You were good enough to show me what ophthalmic data you were collecting. Indeed it is summarised very clearly in Chapter 15 of the manual of operations. Is any one member of the SUPPORT Trial subcommittee taking the lead in checking the accuracy and consistency of the ophthalmic data or is this a task you are all sharing ?

Your data monitoring committee has obviously been doing a thorough and constructive job. Is their identity confidential ? I only ask because I could find nothing about this committee, or its membership, from the copy of the protocol or the Manual of Operations that you let me have, in confidence, several months ago now.

Edmund Hey

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: How is SUPPORT Going ?
Date: Monday, March 20, 2006 10:49:43 AM
Attachments: RE Analysis of first forms.msg
Analysis of first forms.msg

Rose:

Dale did look at some forms and you had a question for her (see attached emails) that I am not sure was answered. After that, we all got side-tracked by the DSMC mess. Let me know if and how you want to move ahead with this issue.

Thanks

Abhik

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 20, 2006 10:35 AM
To: Das, Abhik
Subject: FW: How is SUPPORT Going ?

Abhik
Did Dale review the "first five" Rop forms from each site for SUPPORT? The trial got stopped and I am not sure this happened. It was OK'd by data access as part of a "quality control" measure for the trial.
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, March 20, 2006 10:14 AM
To: 'Edmund Hey'
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: How is SUPPORT Going ?

Hi Edmund
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NEONATAL UPDATE 2006, , 27 November - 1 December 2006 at The Wolfson Conference Centre, Imperial College London.
Perhaps we can meet and discuss any issues you may have at that time.
Be well
Neil

From: Edmund Hey [mailto(b) (6)
Sent: Monday, March 20, 2006 6:33 AM
To: Finer, Neil

Subject: How is SUPPORT Going ?

Neil,

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Your data monitoring committee has obviously been doing a thorough and constructive job. Is their identity confidential ? I only ask because I could find nothing about this committee, or its membership, from the copy of the protocol or the Manual of Operations that you let me have, in confidence, several months ago now.

Edmund Hey

Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, October 07, 2005 12:32 PM
To: Phelps, Dale; Hastings, Betty J.; Das, Abhik
Subject: RE: Analysis of first forms

Dale
Is the issue that the children are not "fully mature" or have an "indeterminate exam" at discharge? We have to get this information.

Thanks
Rose

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Friday, October 07, 2005 12:05 PM
To: Betty Hastings; Abhik Das
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Analysis of first forms

Hi Abhik and Betty,

I have analyzed the 37 forms you sent and written up my opinions in the attached.
The format is neat, easy to 'eyeball' for completeness and outcomes. Thank you.

If these are the final forms and there will be no more updates, we have a problem. 68% have no final outcome.

I thought this should go to you folks first, but then lets think who it should go to next, and what to do about it.

Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
University of Rochester School of Medicine and Dentistry
Division of Neonatology, Pediatrics, Box 651
601 Elmwood Ave
Rochester, NY 14642

(585) 275-2972
FAX (585) 461-3614

Blansfield, Earl (NIH/NICHD) [E]

From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
Sent: Friday, October 07, 2005 12:05 PM
To: Hastings, Betty J.; Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Analysis of first forms
Attachments: QA Review first ROP form SUPP10.doc

Hi Abhik and Betty,

I have analyzed the 37 forms you sent and written up my opinions in the attached.
The format is neat, easy to 'eyeball' for completeness and outcomes. Thank you.

If these are the final forms and there will be no more updates, we have a problem. 68% have no final outcome.

I thought this should go to you folks first, but then lets think who it should go to next, and what to do about it.

Dale

Dale L. Phelps, MD
Professor of Pediatrics and Ophthalmology
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Summary of QA Review of ROP form SUPP10 in the SUPPORT study

Dale L Phelps, MD

Bottom Line:

We do have a problem if the centers do not continue to follow infants following discharge !

Forms

I received by mail 37 form printouts of SUPP10 from 12 centers

The format was easy to read and evaluate, thank you. Some patterns emerged.

Two centers reported examinations after initial status, 10 did not (yet).

11 forms were "Final Complete"

26 forms were not. They were filled in, in part, but did not have sufficient examinations to reach the 'final/acute" complete status.

I am going to guess that two of these forms are infants who expired before getting the rest of their examinations. (as their last examinations were in Zone 1)

Optimistically, we can say that these forms not yet complete and will be updated with more exams as they occur.

or

Pessimistically, 24/35 = 68% of the infants on which I received forms have one of the 2 primary outcomes for this study coded as missing.

One form has what I'm pretty sure is an error. [center 12 Network #74411]

One eye is marked as laser surgery = yes

However the eye findings are zone III, stage 1, no plus.

Surgery would not be indicated for these findings. The fellow eye with the same findings was marked surgery = no

This is a very important error because it would result in this infant being coded as the primary outcome = unfavorable.

We need to work out a 'range check' or cross check on this column. For instance, the column next to it says that the eye did NOT reach criteria for surgery, but then the next column says it did receive surgery. That's a red flag.

The Pattern of "Not Final": Of the 26 forms not a final status

2 where last reported as in zone I (probably infants who have died)

12 where in zone II at the last recorded examination. *Very incomplete.*

8 with no ROP

2 with stage 1 ROP

2 with stage 2 ROP

12 were in zone III at the last recorded examination, but had had only one exam in zone III

4 of these had stage 1 ROP (still very incomplete)

8 had no ROP and had never had any ROP

Some folk may want to argue about these as being final

From: Zaterka-Baxter, Kristin
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Subject: FW: Support materials
Date: Monday, March 20, 2006 8:45:37 AM
Attachments: New Site questions for SUPPORT Trial for infants 241 Completed[1].doc

---

HI,
Please see attached and the email below from Tufts University regarding the new site Support survey.
Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

-----Original Message-----
From: Frantz, Ivan [mailto:IFrantz@tufts-nemc.org]
Sent: Friday, March 17, 2006 9:26 AM
To: Zaterka-Baxter, Kristin; Frantz, Ivan
Cc: Furey, Anne
Subject: RE: Support materials

Attached is the completed SUPPORT DR questionnaire.

-----Original Message-----
From: Zaterka-Baxter, Kristin
To: ifrantz@tufts-nemc.org
Cc: Furey, Anne
Sent: 3/16/2006 4:59 PM
Subject: FW: Support materials

Hi,
Please find attached materials for the SUPPORT training during the upcoming Steering Committee meeting. Please review these materials at your convenience.

Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750

Fax: (919) 485-7762
kzaterka@rti.org

<<SUPPORT Trial Sept 7 04.ppt>> <<Support_Download.ppt>>

03/16/06

New Site questions for SUPPORT Trial for infants 24-28 weeks gestational age:

1. What is your current practice for pulse oximetry ranges? (Where do you try and keep infants in this GA range)
   Lower limit 88
   Upper limit 92

2. What is your current practice for ALARM limits for pulse oximetry (i.e. where does the monitor alarm if the child falls out of range)?
   Lower alarm limit 88
   Upper alarm limit 92

3. Does your site(s) administer surfactant in the delivery room?
   Yes X No
   If yes, at what point in the delivery room?
   Immediate
   Post-stabilization X; usually within 15 minutes
   Age of infant in minutes

4. Does your site(s) use CPAP in the delivery room?
   Yes
   No X
   If yes, list device used

5. Does your site(s) routinely perform antenatal consults on threatened preterm deliveries < 28 weeks?
   Yes X No
   If yes, does the individual performing the consult also consent mothers for research studies?
   Yes
   No X, with rare exceptions
   If No, who obtains research consents? The PI, Co-PI or another neonatologist, but not one directly involved in care of Mom or infant

6. Who attends deliveries of < 28 weeks at your site(s)?
   Attending Neonatologist X
   Attending Hospitalist
   Neonatal Fellow X
   Neonatal Nurse Practitioner
   Neonatal Physician's Assistant
   Pediatric 3rd year Resident
   Pediatric 2nd year Resident X
   Pediatric intern X
   Other Resident (Family medicine, obstetrics, anesthesia, or other)
   Respiratory therapist X
   NICU Nurse X
   Other (state role) Sometimes a NNP is present in place of a pediatric resident

Describe the location of your delivery room/stabilization area with respect to the NICU (do you have a separate room, how far away is it, etc.):
Infants are stabilized in the room where delivery occurs, there is not a separate stabilization area. Stabilization usually consists of thermal management, airway management and administration of

surfactant. Vascular access and medication administration are as per the AAP/ AHA NRP Guidelines. Routine radiographs and vascular access are done in the NICU. Infants are brought to the NICU in a transport incubator. The NICU is located approximately 300 feet from the Labor and Delivery area; the travel time is under 3 minutes.

For infants at approximately 36 weeks post conceptual age, are MRI's routinely done for medical indications?

___ Yes
__X__ No

If MRI's are done, are infants sedated for the procedure?

__X__ Yes
___ No

Does your site use NSIMV for infants who fail CPAP prior to intubation? No.

From: Newman, Jamie
To: Petrie, Carolyn; Betty Vohr; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: Friday call - # enrolled in both SUPPORT and Phototherapy
Date: Wednesday, March 15, 2006 3:00:01 PM

There are 4 babies enrolled in both SUPPORT and Phototherapy: 2 at center 16 and 2 at center 18. See below for their Network ID #'s

Infants enrolled in SUPPORT and Phototherapy

CENTER	NETWORK
16	(b) (6)
16	
18	
18	

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Petrie, Carolyn
Sent: Wednesday, March 15, 2006 12:47 PM
To: Betty Vohr; higginsr@mail.nih.gov
Cc: Newman, Jamie; Das, Abhik; Petrie, Carolyn
Subject: RE: Friday call

Yes, the Miami Gold Standard will be important to discuss.

Also, we must determine a plan for those infants enrolled in both Phototherapy and SUPPORT, since Bayley II is for the PHACT kids and the Bayley III is scheduled for the SUPPORT kids. Jamie will determine the number of kids concurrently enrolled in both studies.

From Betty's previous email:

I have faxed the correlations in the Bayley III manual between the Bayley III and Bayley II scores. They are not strong.

Bayley II Motor with Bayley III combined gross and fine Motor .60
Bayley II MDI with Bayley III receptive and expressive language .71
Those two are about the strongest correlations.

Another item is the certification with the Bayley. Should we set expectations from each center on the minimum number of certified staff and at center and a due date for the certifications?

From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Wednesday, March 15, 2006 12:28 PM
To: higginsr@mail.nih.gov; Petrie, Carolyn
Subject: Friday call

Rose and Carolyn,
I asked Terri Leach to join us on the call. She has some ideas.

She pointed out another issue that will need to be resolved. One of the Gold Standards is at Miami so we will have to identify someone new.

From:	Wally Carlo, M.D.
To:	nfiner@ucsd.edu; Kathleen.Bridges@cchmc.org
Cc:	bkh@rti.org; adas@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
Subject:	Re: SUPPORT alarm question
Date:	Tuesday, March 14, 2006 5:53:43 PM

High alarm limit of 99% may work even better as there will be less alarms but still will pick up when the baby is given O2.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: 'Kathleen Bridges' <Kathleen.Bridges@cchmc.org>
CC: 'Betty Hastings' <bkh@rti.org>; Das, Abhik <adas@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: Tue Mar 14 15:40:23 2006
Subject: RE: SUPPORT alarm question

Hi Kathleen.

Yes, if the baby is on room air and has SpOs > 96% then the high alarm can be defeated – turned off. Some units have chosen to set the high alarm at 98% at that point to prevent the infant from being exposed to increased oxygen if the infant required oxygen again, but the high alarm had been left off. For some infants however, the SpO2 on room air will increase to > 98% and that will necessitate the alarm being turned off

I hope this helps

Neil

From: Kathleen Bridges [mailto:Kathleen.Bridges@cchmc.org]
Sent: Tuesday, March 14, 2006 10:51 AM
To: nfiner@ucsd.edu
Subject: SUPPORT alarm question

Hi,

We just need clarification here at UC on one point. When a baby is on 21% FiO2 (and some form of respiratory support - CPAP, NC, etc...), can the bedside staff disable the high alarm or not?

thanks,

kate

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: wrich@ucsd.edu
Subject: RE: SUPPORT/Appendix F
Date: Tuesday, March 14, 2006 3:32:50 PM

This is fine
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 14, 2006 7:55 AM
To: nfiner@ucsd.edu
Subject: FW: SUPPORT/Appendix F

Neil
The changes were made – are you ok with this version? If not, send back your changes.
Thanks
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, March 14, 2006 10:44 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Hastings, Betty J.
Subject: FW: SUPPORT/Appendix F

Hi,
Please find attached the revised Appendix F based on the email below. Revisions are highlighted. Please note we have made the signature line optional. If you are in agreement with there changes, we will send the appropriate technical memo.
Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 13, 2006 4:15 PM
To: Hastings, Betty J.; Zaterka-Baxter, Kristin
Cc: nfiner@ucsd.edu; Wade Rich
Subject: RE: SUPPORT

Betty
Appendix F – **should only apply to infants receiving oxygen.** The alarms should NOT be disabled for children **in oxygen**

For children in room air, the alarm limits would not need to be set at 96 at the high end. It may need to be

higher and should be left to the discretion of the site.

Also, remove the signature line at the bottom of the form – the group had not wanted that.
Can you send it to Nancy and Michele prior to distribution

Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Monday, March 13, 2006 1:46 PM
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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: SUPPORT

Attached are Appendix F and G for the SUPPORT Manual of Operations. These are the last two changes proposed by Dr. Finer. Also attached is a Technical Memo explaining these Appendices.

Thanks.
Betty

<<SUPPORT SATURATION RANGE final.doc>> <<Appendix F Manage O2 concentrations RBC.doc>> <<SUP07.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SAE Support (b) (6)
Date: Tuesday, March 14, 2006 12:20:34 PM

The second of twins. very very difficult.
wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 14, 2006 9:17 AM
To: wrich@ucsd.edu
Cc: Hastings, Betty J.; nfiner@ucsd.edu
Subject: RE: SAE Support (b) (6)

Wade
Thanks for sending this - if you have access to the autopsy report later on, it can also be submitted. This is always very difficult for the family and the staff - Take care Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, March 14, 2006 12:10 PM
To: 'Hastings, Betty J.'; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SAE Support (b) (6)

Attached please find medwatch and internal SAE report on death (b) (6) at Center 22, Site (b) (6)
Thank you.
wade

From: Wade Rich
To: "Hastings, Betty J."; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SAE Support 23702
Date: Tuesday, March 14, 2006 12:10:10 PM
Attachments: (b) (6) ae.pdf
Medwatch (b) (6) .pdf

Attached please find medwatch and internal SAE report on death (b) (6) at Center 22, Site (b) (6)
Thank you.
wade

This is the information already submitted for this adverse event. Please review it, then scroll to the bottom of the web page to enter your additional information or amendment.

UCSD Human Research Protections Program

Report of Adverse Event

Section 1: Identifying Information				
Project	Number:	041069	Principal Investigator:	Neil Finer
	Title:	The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants The SUPPORT Trial of the NICHD Neonatal Research Network		
Submitter	Name:	Wade Rich, BS, RRT	Phone:	35375
	E-mail:	wrich@ucsd	Mail code:	35375
Adverse Event	Adverse Event ID:	004		
	Date occurred:	03/10/2006	Date known to you:	03/13/2006
	Date submitted:	03/14/2006	Subject's Age:	(b) (6)
	Subject's Study ID:	(b) (6)	Subject's Gender:	Male
	Short title:	Death		
	Name of drug, device or procedure involved:	N/A		

Yes	No	**Section 2: ADVERSE EVENT CHARACTERISTICS**
	X	Event is ongoing as of this report
	X	Resulted in or prolonged **hospitalization**
	X	Resulted in need for **treatment or supportive care**
	X	Resulted in significant **disability**
	X	Associated with **congenital malformation or abnormality**
	X	Is or was **life threatening**
X		Was **fatal**
	X	Participant **remains on study**
	X	**Study blind** was broken
	X	**Risk of this event was present in consent** signed by the person who experienced this event
	X	**Consent will be modified** as a result of this event
	X	**Research plan will be modified** to reduce risk of this event occurring again
	X	Event has been reported to **study sponsor**
	X	Event has been reported to **FDA or other federal regulatory agencies**
	X	Event has been reported to the study **Data and Safety Monitoring Board (DSMB)**

Section 3: PRINCIPAL INVESTIGATOR'S ASSESSMENT OF EVENT	
Likelihood the adverse event was caused by the study:	Probable
	Possible
	Unlikely

5-04459

	X	Definitely Unrelated

Section 4: NARRATIVE DESCRIPTION OF EVENT
Infant died at home at 5 mos. of age. Autopsy report not available, but death is thought to be from SIDS at this time.
NARRATIVE DESCRIPTION OF RESPONSE TO EVENT, including dates and locations of treatment provided
DESCRIPTION OF HOW COSTS, IF ANY, WERE PAID BY SUBJECT, P.I., SPONSOR OR UNIVERSITY
N/A

Enter the text you wish to add to this adverse event report here:

Use as much space as needed:

Submit

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

MEDWATCH FORM

SUPP08A Rel 1.0
January 4, 2005

Center: 22 Site No: (b) (6) Network: (b) (6) Birth: (b) (6) 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: 11/30/98
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: ___ 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 2/10/2006 (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) 3/14/06
5. Describe event or problem

INFANT DISCHARGED HOME ON (b) (6) INFANT WAS RANDOMIZED IN THE SUPPORT TRIAL, IN THE CPAP ARM INFANT DIED AT HOME AT (b) (6) OF ACE OF APPARENT SIDS. AUTOPSY PENDING.

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) (mo/day/yr for 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: WADE RICH
   phone # 617-543-5775
2. Health professional? ☒ yes ☐ no
3. Occupation: CRC/RAT
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. ☐

PLEASE TYPE OR USE BLACK INK

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.

5-04461

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu
Cc: Hastings, Betty J.
Subject: FW: SUPPORT/Appendix F
Date: Tuesday, March 14, 2006 10:45:50 AM
Attachments: APPENDIX F.doc

Hi,
Please find attached the revised Appendix F based on the email below. Revisions are highlighted. Please note we have made the signature line optional. If you are in agreement with there changes, we will send the appropriate technical memo.
Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 13, 2006 4:15 PM
To: Hastings, Betty J.; Zaterka-Baxter, Kristin
Cc: nfiner@ucsd.edu; Wade Rich
Subject: RE: SUPPORT

Betty
Appendix F – **should only apply to infants receiving oxygen.** The alarms should NOT be disabled for children **in oxygen**

For children in room air, the alarm limits would not need to be set at 96 at the high end. It may need to be higher and should be left to the discretion of the site.

Also, remove the signature line at the bottom of the form – the group had not wanted that.
Can you send it to Nancy and Michele prior to distribution

Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Monday, March 13, 2006 1:46 PM
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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: SUPPORT

Attached are Appendix F and G for the SUPPORT Manual of Operations. These are the last two changes proposed by Dr. Finer. Also attached is a Technical Memo explaining these Appendices.

Thanks.
Betty

<<SUPPORT SATURATION RANGE final.doc>> <<Appendix F Manage O2 concentrations RBC.doc>> <<SUP07.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA while receiving supplemental oxygen

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2?
     (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time while receiving supplemental oxygen*

d. Weaning FiO2 and oxygen saturation levels:
   Wean by 2-5% if the saturation is high (>95%).
   - 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.

2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name (optional)

_____

Signature (optional)

_____

Date

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD) [E]; Jamie Newman; Carolyn Petrie
Cc: Jean Steichen; Kimberly Yolton; Kurt Schibler
Subject: Re: Forms for SUPPORT FU babies >1,000g
Date: Tuesday, March 14, 2006 9:32:20 AM

Please add Kim Yolton PhD to the Network Followup email lists. She is helping lead our followup research team.
Thanks.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
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>>> "Newman, Jamie" <newman@rti.org> 03/13/2006 3:31 PM >>>
Attached are the initial forms that you will need for the follow-up of infants enrolled in the SUPPORT Trial that are greater than 1000g. These forms correspond to the GDB ELBW Follow-up forms (NF01, NF02, etc.) except the header information and instructions for completing the
forms are specific to SUPPORT infants greater than 1000g. Attached is the SF01
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Fo

rms/NF01.pdf> (SES at Discharge) as well as the SF10 (Status Form) which should be used for infants that die prior to the 18 month visit. The remaining forms will be distributed closer to when the windows for the 18 month windows start to open. As noted below, these forms will be
entered into the follow-up portion of SUPPORT Trial data entry system which should be distributed later this week along with the Breathing Outcomes data entry system. Please let us know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH

Statistics and Epidemiology

RTI International

Telephone: (919) 485-5719

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newman@rti.org

From: Petrie, Carolyn
Sent: Wednesday, March 08, 2006 1:04 PM
To: Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles Rosenfeld (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; jon.e.tyson@uth.tmc.edu; M. D. Abbot Laptook (alaptook@WIHRI.org); Michele Walsh (mcw3@cwru.edu); moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; William Oh2 (WOh@wihri.org); (Nancy.Miller@UTSouthwestern.edu); ae5357@wayne.edu; ahensman@wihri.org; auten002@mc.duke.edu; ellen_hale@oz.ped.emory.edu; Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); grisbyca@email.uc.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Monica Kontstantino (Monica.konstantino@yale.edu); Nancy Newman (nxs5@cwru.edu); npeters@wfubmc.edu; reverett@med.miami.edu; Wade Rich (wrich@ucsd.edu); (Janet.Morgan@childrens.com); (SEguaras@med.miami.edu); bjacksn@wfubmc.edu; Bonnie Siner (bss5@cwru.edu); diane_hust@urmc.rochester.edu; dkennedy@dmc.org; joanne williams; ldrichar@iupui.edu; lnoel@wihri.org; lohme001@mc.duke.edu; mgfuller@ucsd.edu; MSN Elaine Romano (elaine.romano@yale.edu); Teresa.Gratton@uc.edu; "Vivien Phillips ' (E-mail)'; (Roy.Heyne@utsouthwestern.edu); (ira_adams-chapman@oz.ped.emory.edu); adusick@iupui.edu; Athina Pappas MD (apappas@med.wayne.edu); Brenda.H.Morris@uth.tmc.edu; bvohr@wihri.org; cbauer@peds.med.miami.edu; gary_myers@urmc.rochester.edu; 'golds005@mc.duke.edu'; M. D. Dee Wilson
(b) (6) Myriam Peralta (MPeralta@PEDS.UAB.EDU); rdillard@wfubmc.edu; srhintz@stanford.edu; steichjj@email.uc.edu; yvaucher@ucsd.edu
Cc: Price, Jeffrey M.; Auman, Jeanette O.; Newman, Jamie; Zaterka-Baxter, Kristin; Petrie, Carolyn; Hastings, Betty J.
Subject: Tech memo for SUPPORT FU babies >1,000g

Dear All-

Please find the technical memo attached to this email, pertaining to the
18-22 month Follow Up visit for infants enrolled in SUPPORT and

greater
than 1000g.

Follow-up at 18 months should be completed for all patients enrolled
in
the SUPPORT Trial. The SUPPORT Trial Follow-up will be as follows:

1. All Network patients, eligible for the 18+4 month follow-up should have the GDB ELBW Follow-up forms completed (NF01, NF02, etc.). These forms are entered into the regular GDB Follow-up program.
2. All SUPPORT Trial study patients NOT eligible for the ELBW Network Follow-up Study, such as patients >1000 g, should complete the SUPPORT Follow-up Study forms (e.g., SF01, SF02, etc.). These forms will
be entered into the SUPPORT Trial database.

Because the content of the follow-up is the same, the ELBW Follow-up study manual will be used for the additional SUPPORT Trial study patients, using the following substitutions: NF01 = SF01, NF02 = SF02,
NF03 = SF03, Etc.

The NF13 (BITSEA) will not be done for SUPPORT Trial patients unless they are in the ELBW Follow-up Study. The SUPPORT patients not eligible
for the ELBW Follow-up Study will use their Network number as the identifier. For patients that transfer to another center, the forms will need to be sent to the original center for keying.

The following forms will need to be completed for the SUPPORT Trial patients NOT eligible for ELBW Follow-up Study:

SF01
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Fo

rms/NF01.pdf> SES at Discharge
SF03 SES at 18 + 4 Months
SF04 Medical History Form
SF04A Readmission Form
SF05
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Fo

rms/NF05.pdf> Infant Examination Form
SF05A Gross Motor Function Work Sheet (will not be keyed)
SF09 Bayley Scales Summary Score Sheet
SF10 Status Form
SF10A Status Form
SF11 Summary of 18 Month Visit

SF12 Lost to Follow-up Questionnaire

These forms will be posted to the private gateway of the NRN website under:

Protocols/SUPPORT/Secondary Studies/18 month Follow Up.

Please contact Jamie Newman at newman@rti.org <mailto:newman@rti.org>
or Carolyn Petrie Huitema at petrie@rti.org <mailto:petrie@rti.org>
if
you have any questions.

From: Nancy Peters
To: nfiner@ucsd.edu; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kathy J Auten; Hastings, Betty J.
Subject: RE: SUPPORT and oximeters
Date: Monday, March 13, 2006 5:56:15 PM

Neil,

Thank you

Nancy

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, March 13, 2006 4:18 PM
To: Nancy Peters; Wade Rich; 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: 'Kathy J Auten'; 'Hastings, Betty J.'; Wade Rich; 'Neil Finer'
Subject: RE: SUPPORT and oximeters

Hi Nancy
We did not intend to have high alarms routinely active for children not in oxygen. Rose and I have discussed this and will ask Betty to change the Appendix. In addition we will remove the need to sign this form as we previously had agreed.
Thanks
Neil

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Monday, March 13, 2006 11:43 AM
To: wrich@ucsd.edu; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kathy J Auten; Hastings, Betty J.
Subject: RE: SUPPORT and oximeters

Wade,

Thank you for your quick response. Tech Memo #7 implies that they will be part of the manual so that we will be compliant with the agreed upon DSMC changes. If they are to be used as guidelines and not required then we are less likely to instigate a rebellion. Will there be guidelines for use of the SatShare cables? (e.g. a standard for the averaging times? I know that this was a concern expressed by another coordinator at our last steering committee meeting...)

Nancy

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Monday, March 13, 2006 2:26 PM
To: Nancy Peters; nfiner@ucsd.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: 'Kathy J Auten'; 'Hastings, Betty J.'
Subject: RE: SUPPORT and oximeters

Kathy, Nancy,

First, I think it is important to realize that these are guidelines, and as such can not be tied to deviations. The document is actually written for all infants less than 28 weeks, which in a given center is not equivalent to SUPPORT babies.

If you are not locking your oximeters, you do not need to worry about it. Actually Monica from Yale told me they go into the "home" mode of the oximeter and set the alarms, then password

protect them. I thought this would yield much screaming and yelling, but if that is what they want to do, it prevents alarms from accidentally being changed. I just needed to address the issue for those who did it. To my knowledge, no other center has considered it. And Yale has only one baby enrolled, so they may change practice with time also.

As to the alarm on R/A, I agree with you, but my impression is that Dr. Carlo would not. He would like the alarms on at all times.

This is the OWL document, revised by Nancy N. and Michele Walsh. We suggested signatures from just the PI and Coordinator on a document saying that the information provided in this document had been provided to the sight, and were told by the subcommittee that it was not a good idea. So I am not at all clear who is going to sign this document and how it will be enforced, if at all.

The opinions expressed in this email are my own, without consultation with Neil. We will discuss it further later today.

wade

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Monday, March 13, 2006 11:07 AM
To: nfiner@ucsd.edu; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kathy J Auten; Hastings, Betty J.
Subject: SUPPORT and oximeters

Neil,

Kathy and I would like some clarification regarding a term used in the manual revision, as well as a question about oximeters alarms with infants on RA support.

On pg 10-3 of the latest revision of the manual, first paragraph, line 5: ("Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits.) .....what is the definition of the term "locked"....is this the same as "set"? This is the first time that we can remember seeing a reference to the word "locked" in relation to oximeters in this study.

Have just received the latest tech memo and Appendices so this somewhat answers our other question -- - 0ximeter alarms and infants on RA support. I can't say that I agree that the alarms should not be disabled at any time, we have had infants on RA vent that constantly alarmed as their saturations were 100. I think that it will tend to make staff ignore an alarm when the majority of the time it is occurring because the infant has a high saturation on RA but still requires support so when it is triggered by a low alarm there could be a delay in the response. After reviewing Appendix F though, who do you envision signing this.....the neonatologist?, the NNP?, the RRT?, the RN assigned to this infant for a particular shift? the research staff?, or everyone in the NICU? In addition, if bedside staff are not strictly compliant to recording the oximeters q 4-6 hrs are we required to complete a deviation form for each occurrence?

Nancy

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Nancy Newman; nfiner@ucsd.edu
Cc: nfiner@ucsd.edu; Wade Rich
Subject: RE: SUPPORT
Date: Monday, March 13, 2006 4:18:23 PM

Rose,
Nancy and Michele modified this and I was told this was final. I'll forward your e-mail to them.
Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 13, 2006 4:15 PM
To: Hastings, Betty J.; Zaterka-Baxter, Kristin
Cc: nfiner@ucsd.edu; Wade Rich
Subject: RE: SUPPORT

Betty
Appendix F – **should only apply to infants receiving oxygen.** The alarms should NOT be disabled for children **in oxygen**

For children in room air, the alarm limits would not need to be set at 96 at the high end. It may need to be higher and should be left to the discretion of the site.

Also, remove the signature line at the bottom of the form – the group had not wanted that.
Can you send it to Nancy and Michele prior to distribution

Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Monday, March 13, 2006 1:46 PM
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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject: SUPPORT

Attached are Appendix F and G for the SUPPORT Manual of Operations. These are the last two changes proposed by Dr. Finer. Also attached is a Technical Memo explaining these Appendices.

Thanks.
Betty
<<SUPPORT SATURATION RANGE final.doc>> <<Appendix F Manage O2 concentrations RBC.doc>> <<SUP07.doc>>

Betty Hastings

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From: Newman, Jamie
To: 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; 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; Nancy.Miller@UTSouthwestern.edu; ae5357@wayne.edu; ahensman@wihri.org; auten002@mc.duke.edu; ellen_hale@oz.ped.emory.edu; Georgia.E.McDavid@uth.tmc.edu; grisbyca@email.uc.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Monica.konstantino@yale.edu; nxs5@cwru.edu; npeters@wfubmc.edu; reverett@med.miami.edu; wrich@ucsd.edu; Janet.Morgan@childrens.com; SEguaras@med.miami.edu; bjacksn@wfubmc.edu; bss5@cwru.edu; diane_hust@urmc.rochester.edu; dkennedy@dmc.org; joanne williams; ldrichar@iupui.edu; lnoel@wihri.org; lohme001@mc.duke.edu; mgfuller@ucsd.edu; elaine.romano@yale.edu; Teresa.Gratton@uc.edu; "Vivien Phillips " (E-mail); Roy.Heyne@utsouthwestern.edu; ira_adams-chapman@oz.ped.emory.edu; adusick@iupui.edu; apappas@med.wayne.edu; Brenda.H.Morris@uth.tmc.edu; bvohr@wihri.org; cbauer@peds.med.miami.edu; gary_myers@urmc.rochester.edu; golds005@mc.duke.edu; (b) (6) MPeralta@PEDS.UAB.EDU; rdillard@wfubmc.edu; srhintz@stanford.edu; steichji@email.uc.edu; yvaucher@ucsd.edu; Rosemary_Jensen@URMC.Rochester.edu; Jackie.Benson@sharp.com; Stevens, Timothy
Cc: Auman, Jeanette O.; Zaterka-Baxter, Kristin; Hastings, Betty J.; Petrie, Carolyn
Subject: Forms for SUPPORT FU babies >1,000g
Date: Monday, March 13, 2006 3:31:13 PM
Attachments: SF01 SES at DC_3_13_2006.doc
SF10 Status_3_13_2006.doc

Attached are the initial forms that you will need for the follow-up of infants enrolled in the SUPPORT Trial that are greater than 1000g. These forms correspond to the GDB ELBW Follow-up forms (NF01, NF02, etc.) except the header information and instructions for completing the forms are specific to SUPPORT infants greater than 1000g. Attached is the SF01 (SES at Discharge) as well as the SF10 (Status Form) which should be used for infants that die prior to the 18 month visit. The remaining forms will be distributed closer to when the windows for the 18 month windows start to open. As noted below, these forms will be entered into the follow-up portion of SUPPORT Trial data entry system which should be distributed later this week along with the Breathing Outcomes data entry system. Please let us know if you have any questions.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
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Fax: (919) 485-7762
newman@rti.org

From: Petrie, Carolyn
Sent: Wednesday, March 08, 2006 1:04 PM
To: Poole, W. Kenneth; [SCRN] Stoll, Barbara; Charles Rosenfeld (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; jon.e.tyson@uth.tmc.edu; M. D. Abbot Laptook (alaptook@WIHRI.org); Michele Walsh (mcw3@cwru.edu); moshea@wfubmc.edu; nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; sduara@miami.edu; sshankar@med.wayne.edu; wcarlo@peds.uab.edu; William Oh2 (WOh@wihri.org); (Nancy.Miller@UTSouthwestern.edu); ae5357@wayne.edu; ahensman@wihri.org; auten002@mc.duke.edu; ellen_hale@oz.ped.emory.edu; Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); grisbyca@email.uc.edu; linda_reubens@urmc.rochester.edu; lucmille@iupui.edu; mbball@leland.stanford.edu; mcollins@peds.uab.edu; Monica Kontstantino (Monica.konstantino@yale.edu); Nancy Newman (nxs5@cwru.edu); npeters@wfubmc.edu; reverett@med.miami.edu; Wade Rich (wrich@ucsd.edu); (Janet.Morgan@childrens.com); (SEguaras@med.miami.edu); bjacksn@wfubmc.edu; Bonnie Siner (bss5@cwru.edu); diane_hust@urmc.rochester.edu; dkennedy@dmc.org; joanne williams; ldrichar@iupui.edu; lnoel@wihri.org; lohme001@mc.duke.edu; mgfuller@ucsd.edu; MSN Elaine Romano (elaine.romano@yale.edu); Teresa.Gratton@uc.edu; "Vivien Phillips ' (E-mail)';

(Roy.Heyne@utsouthwestern.edu); (ira_adams-chapman@oz.ped.emory.edu); adusick@iupui.edu; Athina Pappas MD (apappas@med.wayne.edu); Brenda.H.Morris@uth.tmc.edu; bvohr@wihri.org; cbauer@peds.med.miami.edu; gary_myers@urmc.rochester.edu; 'golds005@mc.duke.edu'; M. D. Dee Wilson(b) (6) Myriam Peralta (MPeralta@PEDS.UAB.EDU); rdillard@wfubmc.edu; srhintz@stanford.edu; steichjj@email.uc.edu; yvaucher@ucsd.edu
Cc: Price, Jeffrey M.; Auman, Jeanette O.; Newman, Jamie; Zaterka-Baxter, Kristin; Petrie, Carolyn; Hastings, Betty J.
Subject: Tech memo for SUPPORT FU babies >1,000g

Dear All-

Please find the technical memo attached to this email, pertaining to the 18-22 month Follow Up visit for infants enrolled in SUPPORT and greater than 1000g.

Follow-up at 18 months should be completed for all patients enrolled in the SUPPORT Trial. The SUPPORT Trial Follow-up will be as follows:

1. All Network patients, eligible for the 18+4 month follow-up should have the GDB ELBW Follow-up forms completed (NF01, NF02, etc.). These forms are entered into the regular GDB Follow-up program.
2. All SUPPORT Trial study patients NOT eligible for the ELBW Network Follow-up Study, such as patients >1000 g, should complete the SUPPORT Follow-up Study forms (e.g., SF01, SF02, etc.). These forms will be entered into the SUPPORT Trial database.

Because the content of the follow-up is the same, the ELBW Follow-up study manual will be used for the additional SUPPORT Trial study patients, using the following substitutions: NF01 = SF01, NF02 = SF02, NF03 = SF03, Etc.

The NF13 (BITSEA) will not be done for SUPPORT Trial patients unless they are in the ELBW Follow-up Study. The SUPPORT patients not eligible for the ELBW Follow-up Study will use their Network number as the identifier. For patients that transfer to another center, the forms will need to be sent to the original center for keying.

The following forms will need to be completed for the SUPPORT Trial patients NOT eligible for ELBW Follow-up Study:

SF01 SES at Discharge
SF03 SES at 18 + 4 Months
SF04 Medical History Form
SF04A Readmission Form
SF05 Infant Examination Form
SF05A Gross Motor Function Work Sheet (will not be keyed)
SF09 Bayley Scales Summary Score Sheet
SF10 Status Form
SF10A Status Form
SF11 Summary of 18 Month Visit
SF12 Lost to Follow-up Questionnaire

These forms will be posted to the private gateway of the NRN website under: Protocols/SUPPORT/Secondary Studies/18 month Follow Up.

Please contact Jamie Newman at newman@rti.org or Carolyn Petrie Huitema at

petrie@rti.org if you have any questions.

Center: __ __ Site No: __ Network No: __ __ __ __ Birth Order: __ Mother's Initials: __ __ __

This form should be completed for all infants at the time of discharge to home or to chronic care, who are enrolled in the SUPPORT Trial and > 1000 grams.

A. DEMOGRAPHIC DATA

1. Date of discharge: __ __/__ __/__ __ __ __ (Month Day Year)
2. Date of birth: __ __/__ __/__ __ __ __ (Month Day Year)
3. Age
   a. Chronological age: ___ ___ ___ Weeks
   b. Corrected age: ___ ___ ___ Weeks
4. Will the child be under state supervision? Y N
5. Primary caretaker: ___ ___ ___
(Parent/Legal Guardian, person who is primarily responsible for parenting the child)
(See Relationship Codes—if biological mother, code is 001)
6. Other caretaker: ___ ___ ___
(See Relationship Codes. If no other caretaker, leave data field blank)
7. Primary Caretaker's marital status: ___

1=Married	3=Divorced
2=Single	4=Widowed

B. HOUSEHOLD COMPOSITION

1. Baby's planned living arrangements: ___ ___
(See Living Arrangement Codes)

IF BABY'S PLANNED LIVING ARRANGEMENTS ARE CODES 16, 17, 18 OR 19, SKIP TO C.7 OF THIS FORM.

2. Number of people living in baby's household: ___ ___

C. EDUCATION AND OCCUPATION

1. Apart from the Primary Caretaker, do others contribute money to the child's household? Y N
2. Highest grade completed or attended:
   a. Primary Caretaker ___
   b. Other Caretaker ___

1=< 7th grade	5=Partial college
2=7th to 9th grade	6=College degree
3=10th to 12th grade	7=Graduate degree
4=High School degree	8=Unknown

3. Currently working
   a. Primary Caretaker? Y N
   b. Other Caretaker? Y N NA
4. Currently in school
   a. Primary Caretaker? Y N
   b. Other Caretaker? Y N NA
5. What is the total income in the baby's household from all sources over the last year? ___

1=<$5,000	5=$30,000 to $39,999
2=$5,000 to $9,999	6=$40,000 to $49,999
3=$10,000 to 19,999	7=$50,000 to $74,999
4=$20,000 to $29,999	8=>$75,000

6. Baby's medical insurance: ___

1=Public	4=Uninsured
2=Private (Employment/purchased)	5=Unknown
3=Both Public and Private	

D. FORM COMPLETION

1. Where was interview conducted: ___

   1=Clinic 3=Telephone 9=Other
   2=Home 4=Hospital

2. Date of SES interview: __ __/__ __/__ __ __ __
   Month Day Year

3. Initials of person administering SES at Discharge: ___ ___ ___

Center: __ __ Site No: __ Network No: __ __ __ __ Birth Order: __ Mother's Initials: __ __ __

This form should be completed for all children at the 18 + 4 month visit who are enrolled in the SUPPORT Trial and > 1000 grams.

A. STATUS INFORMATION

1. Date of birth: __ __/__ __/__ __ __ __
   Month Day Year

2. Final Status of Child: ___

1=Child seen, 18 month visit completed
3=Died after initial discharge to home
4=Lost to follow-up
5=18 Month visit completed at another NICU Network center
6=Child seen, but incomplete visit

IF 18 MONTH VISIT IS COMPLETED AS MUCH AS POSSIBLE, FILL OUT FORM NF11.

a. If final status is, died after initial discharge to home (3):
   1. Date of death __ __/__ __/__ __ __ __
      Month Day Year

b. If final status is lost to follow-up (4):
   1. Give reason lost to follow-up: ___

1=Adopted	4-Refused informed consent for FU
2=Out of area	5=Non compliant
3=Lost	6=Foster care

B. FORM COMPLETION

1. Date form completed: __ __/__ __/__ __ __ __
   Month Day Year

2. Center number where child was seen: ___ ___ ___

3. Initials of person completing this form: ___ ___ ___

From:	Hastings, Betty J.
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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject:	SUPPORT
Date:	Monday, March 13, 2006 1:45:59 PM
Attachments:	SUPPORT SATURATION RANGE final.doc Appendix F Manage O2 concentrations RBC.doc SUP07.doc

---

Attached are Appendix F and G for the SUPPORT Manual of Operations. These are the last two changes proposed by Dr. Finer. Also attached is a Technical Memo explaining these Appendices.

Thanks.
Betty

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Betty Hastings

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APPENDIX G

SUPPORT
SATURATION RANGE
GOAL 85-95%
IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	2-5%
<70	30 sec.	5%

APPENDIX F

Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the infant<28 wk GA

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
2. No 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 is a drug with potentially toxic side effects. Too much can be as damaging as too little. There is no evidence that <28 week infants need saturations in the 95-100% range (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of <28 week infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2? (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. Note that Masimo alarms go off at the set value. Thus, these alarm settings are equivalent to alarms commonly set at 85% and 95% on other pulse oximeters. *The alarms should not be disabled at any time*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).

- 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 and saturation levels:
Increase the FiO2 by 2-5% if the saturation is low (<85%).

- When an increase is needed in the FiO2, the person making the change should stay with the infant until the infant has reached a stable saturation level.
- 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
- Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
- Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
- Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.
2. 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 should 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name

_____

Signature

_____

Date

RTI INTERNATIONAL | Memorandum

March 13, 2006

SUPPORT TECHNICAL MEMO # 7

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Appendix F and G of the Manual of Operations for the SUPPORT Trial

In order to be compliant with the changes as proposed by Dr. Finer, and agreed upon by the DSMC, attached are the last of the two items that were proposed by Dr. Finer. The following will be incorporated into the manual of operations as Appendix F and G.

- Appendix F—A document on Management of Oxygen Concentrations and Oxygen Saturations in the Infant <28 weeks Gestational Age
- Appendix G—An example of a Bedside Card with the Support Saturation Range (Desired Goal)

The appendices are attached and the final MOP and forms will be posted on the Neonatal Web site.

cc: Rosemary Higgins

From:	Wade Rich
To:	"Hastings, Betty J."; nfiner@ucsd.edu; sduara@miami.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; edward.donovan@chmcc.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Zaterka-Baxter, Kristin"; ahensman@wihri.org; "Nancy Newman"
Subject:	RE: SUPPORT
Date:	Thursday, March 09, 2006 2:59:10 PM

Nancy/Michele,
Thanks for doing this. If this is a document we will be using for our SUPPORT babies, it should probably say that, rather than all infants under 28 weeks. If it is a change in
Network practice for all babies under 28 weeks, I would think more the our subcommittee need to approve it, and perhaps it should be in GDB.
Also, I see no Sat Range card attached.
wade

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, March 09, 2006 11:29 AM
To: nfiner@ucsd.edu; sduara@miami.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; edward.donovan@chmcc.org
Cc: higginsr@mail.nih.gov; Das, Abhik; Zaterka-Baxter, Kristin; ahensman@wihri.org; Nancy Newman; wrich@ucsd.edu
Subject: SUPPORT
Importance: High

Dear SUPPORT Subcommittee,

Please review the attached document on the **Management of Oxygen Concentrations and Oxygen Saturations in the VLBW Infant (<28 weeks Gestational Age).** Michele Walsh and Nancy Newman have revised the old version of the "OXYGEN WITH LOVE" document (that was distributed earlier) in order to meet the study guidelines of the SUPPORT study. If you have no objections to this revised document, it will be incorporated into the MOP.

Also attached is copy of the **SUPPORT SATURATION RANGE BEDSIDE CARD.** This will also be added to the MOP.

Thanks for your review of both of these documents.
Betty

<<SUPPORT SATURATION RANGE[mw edit (2)].doc>> <<Appendix F Manage O2 concentrations RBC.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740

Fax: (919) 485-7762
bkh@rti.org

From:	Hastings, Betty J.
To:	nfiner@ucsd.edu; sduara@miami.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; edward.donovan@chmcc.org
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Zaterka-Baxter, Kristin; ahensman@wihri.org; Nancy Newman; wrich@ucsd.edu
Subject:	SUPPORT
Date:	Thursday, March 09, 2006 2:35:57 PM
Attachments:	SUPPORT SATURATION RANGE[mw edit (2)].doc Appendix F Manage O2 concentrations RBC.doc
Importance:	High

Dear SUPPORT Subcommittee,

Please review the attached document on the **Management of Oxygen Concentrations and Oxygen Saturations in the VLBW Infant (<28 weeks Gestational Age).** Michele Walsh and Nancy Newman have revised the old version of the "OXYGEN WITH LOVE" document (that was distributed earlier) in order to meet the study guidelines of the SUPPORT study. If you have no objections to this revised document, it will be incorporated into the MOP.

Also attached is copy of the **SUPPORT SATURATION RANGE BEDSIDE CARD.** This will also be added to the MOP.

Thanks for your review of both of these documents.
Betty

<<SUPPORT SATURATION RANGE[mw edit (2)].doc>> <<Appendix F Manage O2 concentrations RBC.doc>>

Betty Hastings

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SUPPORT

SATURATION RANGE

GOAL 85-95%

IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	4-5%
<70	30 sec.	5%

Management of Oxygen Concentrations and Oxygen Saturations in the VLBW Infant (<28 weeks Gestational Age)

OBJECTIVE: To avoid hyperoxia and high/low swings in oxygen saturations in the Very Low Birth Weight (VLBW) infant. (<28 wk GA)

1. Initiate the protocol with the admission of each infant with GA less than 28 weeks at birth.
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 is 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 (while receiving supplemental oxygen) and these levels are potentially dangerous. Alternating episodes of hypoxia and hyperoxia can cause significant alterations in the vascular tone of VLBW infants.

b. Saturation alarms:
   1. Assess the validity of the alarm:
   - Is the pulse wave appropriate?
   - Is there artifact interference?
   - Has the saturation been down low enough for long enough to warrant an increase in FiO2? (see Desaturation Management Guidelines)

c. Alarm settings: The alarms should be set at 84% and 96%. *The alarms should not be disabled at any time*

d. Weaning FiO2 and oxygen saturation levels:
Wean by 2-5% if the saturation is high (>95%).
   - 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 the infant has reached a stable saturation level.
   - 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. Individual infants may require modest increases (5-10%) if they tolerate handling poorly. 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 their previously stable baseline.
   - Consider that other settings (rate, PIP, PEEP) may need to be changed for a prolonged procedure.

g. Spontaneous oxygen desaturations:
   - Assess both the infant and the ventilator and/or oxygen delivery systems.

h. Apnea:
   - Choose the appropriate response based on assessment of the infant; increase respiratory rate, increase the approved parameters, 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:

1. Set oxygen saturation monitor alarm limits at 84 and 96%.
2. 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.

I certify that I have read the above practice plan and agree to follow the objectives and statements of practice when caring for infants in the NICU.

_____

Printed Name

_____

Signature

_____

Date

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: Growth Secondary
Date: Wednesday, March 08, 2006 12:03:43 PM

Hi Rose, I'll send out the Growth study shortly.

The PD is a bit complicated in that it is now included in the GDB for sites who do the BPD and part of clinical care so that RTI can receive the data. For sites who do not do the BPD as part of clinical care, we have separate study documents including a model consent (actually from Rochester because Case does not require one). These documents can also used in conduction with any potential future NICHD study that is not a part of the GDB but that has BPD and either a primary or secondary outcome (i.e., IPGE possibly)

Margo Brinkley just gave me the NRN passwords for the new sites. Once the Support revisions are final (later this week) I was thinking of calling the sites with these passwords (and follow up with a fed-ex'd letter), then giving them location instructions on where to find the study documents for Support, EOS, and PD. It avoids numerous large emails but also causes somewhat of a delay. What would you prefer?
Thanks again,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, March 08, 2006 8:43 AM
To: Zaterka-Baxter, Kristin
Subject: RE: Growth Secondary

The growth study can go out to the current sites (including Miami, UCSD, Wake and Rochester – any child enrolled until the end of the month can participate at these sites). Yes, we do need to send the physiologic definition as well. I had thought that was part of GDB?
Thanks
Rose

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, March 07, 2006 5:01 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Growth Secondary

Please ignore the recent phone message about the growth study. I was confused. I received the amended versions of the growth study from Shahnaz and I guess the sites will submit this as an addendum to the SUPPORT study and add the appropriate language in that consent as there is no separate consent planned for this study. If that's ok, I will send them out to the current sites. When sending the Support study to the new sites, should I also send the MRI, Antenatal, Breathing Outcomes (first questionnaire is done at discharge) and Growth secondaries? I think I also need to send the Physiologic Def. Study as well?

Thanks,
Kris

From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Monday, November 21, 2005 3:41 PM
To: Zaterka-Baxter, Kristin
Subject: RE: Growth Secondary

I will be submitting as an addendum, and include this is my consent as part of standard of care since our nursery do these measurements except for the length and we are going to train some of the nurses to use the length board with our assistance to do the measurements they need for their NICU care. If the IRB request something different I will let you know.

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, November 18, 2005 2:37 PM
To: Everett, Ruth
Subject: Growth Secondary

Hi Ruth – hope your trip home was a good one!

Re. the Growth Secondary, how are you planning on submitting this to your IRB (i.e., as a modification to the SUPPORT study) and will there be an informed consent for this substudy? I'm not sure of we actually discussed that at the mtg.

Thanks,
Kris

Kristin Zaterka-Baxter, RN, BSN, CCRP
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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:	Hastings, Betty J.
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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.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; 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; Maynard.Rasmussen@sharp.com; mcw3@cwru.edu; Nirupama_Laroia@URMC.Rochester.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@UTSouthwestern.edu; dale_phelps@urmc.rochester.edu; richard.ehrenkranz@yale.edu; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.; Poole, W. Kenneth; Zaterka-Baxter, Kristin; nfiner@ucsd.edu
Subject:	SUPPORT
Date:	Tuesday, March 07, 2006 3:22:01 PM
Attachments:	SUP06.doc Chapter 16[Rev3-7-06].doc Chapter 10[Rev 3-7-06].doc SUPP11[Rev 3-7-06] .doc SUPP05ASafetyMonitor[Rev3-7-06.doc SUPP05SafetyMonitor[Rev3-7-06].doc

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Attached please find the following:

- Technical Memo SUP06
- Revised Chapter 10 and 16 of the Manual of Operations
- Revised SUPP05, SUPP05A and SUPP11.

Please let us know if you have questions about this material.
Thanks.
Betty <<SUP06.doc>> <<Chapter 16[Rev3-7-06].doc>> <<Chapter 10[Rev 3-7-06].doc>> <<SUPP11[Rev 3-7-06] .doc>> <<SUPP05ASafetyMonitor[Rev3-7-06.doc>> <<SUPP05SafetyMonitor[Rev3-7-06].doc>>

Betty Hastings

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bkh@rti.org

RTI INTERNATIONAL | Memorandum

March 7, 2006

SUPPORT TECHNICAL MEMO # 6

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Revised Forms and Manual of Operations for the SUPPORT Trial

In order to be compliant with the changes as proposed by Dr. Finer, and agreed upon by the DSMC, the following changes have been incorporated into the forms and manual of operations:

- Documentation that the oximeters alarm limits are functional per protocol every 4-6 hours.
- Changes to the data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.

Attached are the revised Manual of Operations (Chapters 10 and 16) and the SUPP05, SUPP05A and SUPP11 forms. Please note that we will be making some changes to the Appendices to the MOP and they will be sent out later this week.

cc: Rosemary Higgins

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 to be completed daily from study day 15 through 36 weeks or status, whichever comes first.

Record the following information four times for each day. **Note**: the scheduled time points for each day are collected down each column

- **Date**
  Record the date corresponding to the Study day
- **Scheduled Time:**
  Record a - d for each study day for the scheduled time points 06:00, 12:00, 18:00, 23:59.
- **Highest Level of Support**
  Record the highest level of support the infant is in on at the scheduled time points during this **STUDY** day.
  Enter: 1= HFV, 2=CV, 3= Nasal SIMV, 4= CPAP, 5= NC, 6= Hood, 7= No Support,
- **Oxygen -Yes/No**
  Record "Yes" if the infant was on oxygen at the scheduled time point during the day. Disregard any temporary increases in FiO_2 for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous FiO_2 in a reasonable amount of time (≤ 30 minutes).
  Record "No" if the infant is not in oxygen on this day.
- **Flow rate (Nasal Cannula only)**
  Record the highest flow rate the infant was on at the scheduled time-during the study day. Disregard any temporary increases in flow for desaturation episodes, apnea, bradycardia or procedures where the infant returns to his/her previous flow rate in a reasonable amount of time (≤ 30 minutes)***Flow rate should be recorded **only** if the infant was on a nasal cannula that day. For purposes of recording, Vapotherm is considered a cannula.
- **Oximeter Alarm Check**
  Record the time the oximeter alarm check was done.
  The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to

fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

Chapter 10

Safety Monitoring Form
SUPP05 and SUPP05A

10.1 Introduction

The SUPP05 form will collect respiratory data for Study Days 1-14 to monitor progress of the infant. The SUPP05A will monitor the incidence of intubation/extubations for each Study Day 1-14.

10.2 Instructions for completing the Safety Monitoring Form (SUPP05)

The purpose of this form is to record daily respiratory information **for each study day while infant is in the network hospital**. This form should be completed starting with DOL1 (study day 1) through DOL 14 (study day 14) and information recorded will be based on the calendar day and 24 hour clock.

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 results, FiO_2 and Mode of Support closest to the scheduled times will be recorded.

Record results of blood gas analyses done at 3 daily time points closest to 08:00, 16:00, and 23:59. **If no blood gases were measured during any of the scheduled time, record the FiO_2 and the Mode of Support.** In addition, the FiO_2 and Mode of Support will be recorded every 2 hours closest to 02:00, 04:00, 06:00, 08:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, 22:00 and 23:59.

a. Scheduled Time

The scheduled time is given on the first column of the table. A scheduled time is assigned for a 24 hour period. The scheduled times are labeled as:

1. Scheduled Time: 02:00
2. Scheduled Time: 04:00
3. Scheduled Time: 06:00
4. Scheduled Time: 08:00
5. Scheduled Time: 10:00
6. Scheduled Time: 12:00
7. Scheduled Time: 14:00
8. Scheduled Time: 16:00
9. Scheduled Time: 18:00
10. Scheduled Time: 20:00
11. Scheduled Time: 22:00
12. Scheduled Time: 23:59

b. Time Measured

For blood gas information record the actual 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 8:00~~am~~ the next day) enter the blood gas on the earlier of the selected times and enter ** : ** for the later one. 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.

For all other time points enter the FiO_2 and Mode of Support.

c. pH

Record the acid base status of the blood.

d. $C0_2$

e. PO_2:

f. FiO_2

Record the **FiO_2** at the time the blood gas was collected or at other scheduled time points.

g. Source:

Record the source of the blood gas

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

i. If Mode =5 record Flow Rate

Record the flow rate for infants on nasal cannula

4. If Mode of Support =4 (CPAP), type used:

Record the type of CPAP

2= Ventilator
4= Bubble
6= Flow Driver
9 = Other

13. Oximeter Alarm Check.

The alarm checks should be recorded every 6 hours. Each center can use a 6 hours schedule that best fits their NICU's routine.

The purpose of the oximeter alarm checks is to verify that alarms are being used and will be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guideline

14. 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

15. Was the infant intubated or extubated on this day?
If Yes, Complete Section B and/or Section C of the SUPP05A

10.2.2 Section B. Intubated/Extubated Information on the SUPP05A Form (For NICU ONLY)

This form should be completed if Question 15 on the SUPP05 is coded **"Yes".** If more than one intubation/extubation occurs in one day, complete Section C. Record the intubation/extubation history if needed for each Study Day 1- 14. If the infant did not have an intubation/extubation on a study day, do not complete SUPP05A.

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 information 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
   4. Saturation

10.2.3 Section C. Intubation/Extubation Information (For NICU ONLY) If more than one intubation/extubation occurs in one day, complete Section C.

Record the intubation/extubation history for each Study Day 1- 14.

1. Did the infant have more than one intubation/extubation on this day?
If Yes,
2. 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 information 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.

3. 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
   4. Satration

NOTE: If more than two intubations/extubations were performed, complete additional SUPP05A, Section C for this study day.

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	15 __ __/__ __/__ __ __ __ Month Day Year	16 __ __/__ __/__ __ __ __ Month Day Year	17 __ __/__ __/__ __ __ __ Month Day Year	18 __ __/__ __/__ __ __ __ Month Day Year	19 __ __/__ __/__ __ __ __ Month Day Year	20 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO	YES / NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __ Report No. __ __

This form should be completed if Question 15 on the SUPP05 was coded Yes.

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 __ __ __

C. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

1. Did infant have more than one intubation/extubation on this day? Y N

   If Yes,

2. 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

      _____
3. 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 __ __ __

NOTE: If more than two intubations/extubations were performed, complete additional SUPP5A, Section C for this study day.

Initials of person completing this form: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP-05 Rel 3.0
October 3, 2005
Revised March 7, 2006

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __

Complete a form each day through DOL 14

1. Study Day: __ __ 2. Date: __ __ / __ __ / __ __ __ __.

A. Record blood gas results, FiO_2 and Respiratory Support closest to the Scheduled Time. 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	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __				__. __		___	__. __ __	___
2. 04 : 00	__ __ : __ __				__. __		___	__. __ __	___
3. 06 : 00	__ __ : __ __				__. __		___	__. __ __	___
4. 08 : 00	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	___	___	__. __ __	___
5. 10 : 00	__ __ : __ __				__. __		___	__. __ __	___
6. 12 : 00	__ __ : __ __				__. __		___	__. __ __	___
7. 14 : 00	__ __ : __ __				__. __		___	__. __ __	___
8. 16 : 00	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	___	___	__. __ __	___
9. 18 : 00	__ __ : __ __				__. __		___	__. __ __	___
10. 20 : 00	__ __ : __ __				__. __		___	__. __ __	___
11. 22 : 00	__ __ : __ __				__. __		___	__. __ __	___
12. 23 : 59	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	___	___	__. __ __	___

13. Oximeter Alarm Check (record every 6 hours)

a. __ __ : __ __ Hr Min b. __ __ : __ __ Hr Min c. __ __ : __ __ Hr Min d. __ __ : __ __ Hr Min

14. Was a replacement study oximeter placed on this infant on this day? Y N

If Yes,

a. Serial number: __ __ __ __ __ __

*Source 1= Arterial 2= Venous 3 = Capillary

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

***CPAP Type 2= Ventilator 4= Bubble 6 = Flow Driver 9= Other

15. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

From: Petrie, Carolyn
To: Betty Vohr; Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie
Cc: Das, Abhik
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g
Date: Tuesday, March 07, 2006 1:19:29 PM
Attachments: SUPPORT FU tech memo1.doc

At some point we must instruct the sites on how to prepare in seeing the kids over 1000g. This memo includes not only the NF01 but also the other assessments such as not collecting the BITSEA. Currently about 80 patients have been enrolled, alive and are over 1000g. Their windows will open this fall.

From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Tuesday, March 07, 2006 12:54 PM
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

I do think it would be appropriate to send an initial e-mail message regarding the NF01. We dont want sites to say they didn't know.

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tuesday, March 07, 2006 9:23 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie; Betty Vohr
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

My concern is that we need to remind folks to collect NF01 data on these kids. Therefore we should probably send them some information relatively soon, addressing the over 1000g babies.

We can address the Bayley III as a general Follow Up study update.

Please advise

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 06, 2006 3:00 PM
To: Newman, Jamie; Betty Vohr
Cc: Petrie, Carolyn
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

I think we need to have the Bayley III issue settled first.

The first baby's window will open in December – can we wait a month or two?
Thanks
Rose

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, March 06, 2006 2:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr
Cc: Petrie, Carolyn
Subject: Please review: Tech memo for SUPPORT FU babies >1,000g

Rose and Betty,
Please let us know if you have anything else to add to the attached memo for the SUPPORT Follow-up at 18 months which states how to proceed with the babies greater than 1,000g. Once we get your "go ahead" we will distribute to the larger group. It has already been reviewed by Abhik, Jenny Auman, and

Betty Hastings.

Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

RTI INTERNATIONAL | Memorandum

SUPPORT FOLLOW-UP TECHNICAL MEMO # 1

DATE: March 6, 2006

TO: Network Follow-up PIs and Coordinators
SUPPORT Trial PIs and Coordinators

FROM: The Data Coordinating Center

SUBJECT: SUPPORT 18 month Follow-up

Follow-up at 18 months should be completed for all patients enrolled in the SUPPORT Trial. The SUPPORT Trial Follow-up will be as follows:

1. All Network patients, eligible for the 18+4 month follow-up should have the GDB ELBW Follow-up forms completed (NF01, NF02, etc.). These forms are entered into the regular GDB Follow-up program.
2. All SUPPORT Trial study patients NOT eligible for the ELBW Network Follow-up Study, such as patients >1000 g, should complete the SUPPORT Follow-up Study forms (e.g., SF01, SF02, etc.). These forms will be entered into the SUPPORT Trial database.

Because the content of the follow-up is the same, the ELBW Follow-up study manual will be used for the additional SUPPORT Trial study patients, using the following substitutions: NF01 = SF01, NF02 = SF02, NF03 = SF03, Etc.

The NF13 (BITSEA) will not be done for SUPPORT Trial patients unless they are in the ELBW Follow-up Study. The SUPPORT patients not eligible for the ELBW Follow-up Study will use their Network number as the identifier. For patients that transfer to another center, the forms will need to be sent to the original center for keying.

The following forms will need to be completed for the SUPPORT Trial patients NOT eligible for ELBW Follow-up Study:

SF01 SES at Discharge
SF03 SES at 18 + 4 Months
SF04 Medical History Form
SF04A Readmission Form
SF05 Infant Examination Form
SF05A Gross Motor Function Work Sheet (will not be keyed)
SF09 Bayley Scales Summary Score Sheet
SF10 Status Form
SF10A Status Form
SF11 Summary of 18 Month Visit
SF12 Lost to Follow-up Questionnaire

These forms will be posted to the private gateway of the NRN website under: Protocols/SUPPORT/Secondary Studies/18 month Follow Up.

RTI INTERNATIONAL | **Memorandum**

Please contact Jamie Newman at newman@rti.org or Carolyn Petrie Huitema at petrie@rti.org if you have any questions.

Cc: Rosemary Higgins

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g
Date: Tuesday, March 07, 2006 11:39:33 AM

Do you mean respectively

Phototherapy = Bayley II
SUPPORT = Bayley III

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 07, 2006 11:33 AM
To: Petrie, Carolyn
Subject: Re: Please review: Tech memo for SUPPORT FU babies >1,000g

Please say "late Fall" and clarify the for randomized cohorts
(phototherapy, SUPPORT that bayley II and Bayley III) will be used for
the entire group.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Petrie, Carolyn <petrie@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Tue Mar 07 11:24:05 2006
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

Ok, let me run the email by you before I send:

The NRN 18-22 month Follow Up Study will transition from the Bayley II
to the Bayley III by Fall of this year.

Network centers will be funded to send two staff members who will
perform the Bayley at your center to this training.

Currently we would like to schedule the one-day training for Thursday,
July 19th (the day after our July Steering Committee meeting). It will
be held at or near the Bolger Center in Potomac, MD.

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g
Date: Tuesday, March 07, 2006 11:10:17 AM

Rose-

Should I wait until we get some feedback from betty before I email the group on training?

Or shall I just go ahead and drop the bomb?

From: Betty Vohr [mailto:BVohr@WIHRI.org]
Sent: Monday, March 06, 2006 3:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie
Cc: Petrie, Carolyn
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

We get our Bayley III with video this Friday. Will be able to give you feedback aftery it is reviewed

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 06, 2006 3:00 PM
To: Newman, Jamie; Betty Vohr
Cc: Petrie, Carolyn
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

I think we need to have the Bayley III issue settled first.

The first baby's window will open in December – can we wait a month or two?
Thanks
Rose

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, March 06, 2006 2:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr
Cc: Petrie, Carolyn
Subject: Please review: Tech memo for SUPPORT FU babies >1,000g

Rose and Betty,
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Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From:	Newman, Jamie
To:	Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr; Das, Abhik
Cc:	Petrie, Carolyn
Subject:	RE: Please review: Tech memo for SUPPORT FU babies >1,000g
Date:	Monday, March 06, 2006 3:04:24 PM

Certainly, no problem.

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) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 06, 2006 3:00 PM
To: Newman, Jamie; Betty Vohr
Cc: Petrie, Carolyn
Subject: RE: Please review: Tech memo for SUPPORT FU babies >1,000g

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Sent: Monday, March 06, 2006 2:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr
Cc: Petrie, Carolyn
Subject: Please review: Tech memo for SUPPORT FU babies >1,000g

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Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Hastings, Betty J.
To: ahensman@wihri.org; grisbyca@email.uc.edu; mbball@leland.stanford.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; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT
Date: Monday, March 06, 2006 3:32:36 PM

Thanks very much for all the comments we have received regarding the revised forms. There were several questions regarding the alarm checks.

To clarify: The purpose of the oximeter alarm checks is to verify that alarms are being used. The DSMC did not request this information but Neil felt that this would be a measure of compliance of the protocol (i.e. to verify that the alarm limits are in place). The time points (q6h) can vary at each center but attempts should be made to use a 6 hour schedule. That is why the times are left open to fit each centers routine. Regardless whether the alarms are locked or not, we want to document that caregivers are noting alarm limits. We hope that this will increase awareness of the need for the limits to remain in place. And if changes are needed to the alarm limits, they should be made according to the study guidelines.

We hope this helps to answer your questions. The revised forms and MOP will be forthcoming (hopefully this week).
Thanks.
Betty

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Newman, Jamie
To: Higgins, Rosemary (NIH/NICHD) [E]; Betty Vohr
Cc: Petrie, Carolyn
Subject: Please review: Tech memo for SUPPORT FU babies >1,000g
Date: Monday, March 06, 2006 2:51:37 PM
Attachments: SUPPORT FU tech memo1.doc

Rose and Betty,
Please let us know if you have anything else to add to the attached memo for the SUPPORT Follow-up at 18 months which states how to proceed with the babies greater than 1,000g. Once we get your "go ahead" we will distribute to the larger group. It has already been reviewed by Abhik, Jenny Auman, and Betty Hastings.

Thanks, Jamie

Jamie E. Newman, MPH
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newman@rti.org

RTI INTERNATIONAL | Memorandum

SUPPORT FOLLOW-UP TECHNICAL MEMO # 1

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TO: Network Follow-up PIs and Coordinators
SUPPORT Trial PIs and Coordinators

FROM: The Data Coordinating Center

SUBJECT: SUPPORT 18 month Follow-up

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These forms will be posted to the private gateway of the NRN website under: Protocols/SUPPORT/Secondary Studies/18 month Follow Up.

RTI INTERNATIONAL | **Memorandum**

Please contact Jamie Newman at newman@rti.org or Carolyn Petrie Huitema at petrie@rti.org if you have any questions.

Cc: Rosemary Higgins

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Cc: "Zaterka-Baxter, Kristin"; wrich@ucsd.edu
Subject: RE: New Site questions for SUPPORT Trial for infants 24
Date: Monday, March 06, 2006 2:44:09 PM
Attachments: New Site questions for SUPPORT Trial for infants 24.doc

---

Hi Rose
We have made a few changes and this looks OK
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, March 06, 2006 10:43 AM
To: Neil Finer; wrich@ucsd.edu
Cc: Zaterka-Baxter, Kristin
Subject: New Site questions for SUPPORT Trial for infants 24

Neil and Wade,
Take a look at this and see if I have captured the essence of what is needed from new sites? Once we have it final, we can send it out and get the responses to you in advance of the meeting.

Thanks
Rose
<<New Site questions for SUPPORT Trial for infants 24.doc>>

New Site questions for SUPPORT Trial for infants 24-28 weeks gestational age:

1. What is your current practice for pulse oximetry ranges? (Where do you try and keep infants in this GA range)
   Lower limit _____
   Upper limit _____
2. What is your current practice for ALARM limits for pulse oximetry (i.e. where does the monitor alarm if the child falls out of range)?
   Lower alarm limit_____
   Upper alarm limit _____
3. Does your site(s) administer surfactant in the delivery room?
   Yes___ No___
   If yes, at what point in the delivery room?
   Immediate_____
   Post-stabilization _____
   Age of infant in minutes _____
4. Does your site(s) use CPAP in the delivery room?
   Yes ___
   No ___
   If yes, list device used _____
5. Does your site(s) routinely perform e-antenatal consults on threatened preterm deliveries < 28 weeks?
   Yes ___ No___
   If yes, does the individual performing the consult also consent mothers for research studies?
   Yes ___
   No___
   If No, who obtains research consents? _____
6. Who attends deliveries of < 28 weeks at your site(s)?
   Attending Neonatologist _____
   Attending Hospitalist _____
   Neonatal Fellow_____
   Neonatal Nurse Practitioner_____
   Neonatal Physician's Assistant_____
   Pediatric 3rd year Resident _____
   Pediatric 2nd year Resident_____
   Pediatric intern_____
   Other Resident (Family medicine, obstetrics, anesthesia, or other)_____
   Respiratory therapist_____
   NICU Nurse_____
   Other (state role)_____

Describe the location of your delivery room/stabilization area with respect to the NICU (do you have a separate room, how far away is it, etc.): _____

_____

For infants at approximately 36 weeks post conceptual age, are MRI's routinely done for medical indications?

___ Yes
___ No

If MRI's are done, are infants sedated for the procedure?

___ Yes
___ No

Does your site use NSIMV for infants who fail CPAP prior to intubation?

From:	Avroy Fanaroff
To:	nfiner@ucsd.edu
Cc:	"Michele Walsh"; "Fanaroff, Avroy"; "Carlo, Wally"; "Donovan, Edward (DONOVAEF)"; "Duara, Shahnaz"; "Goldberg, Ron"; Higgins, Rosemary (NIH/NICHD) [E]; "Jobe, Alan"; "Laptook, Abbot"; "Oh, William"; "Poole, Ken"; "Rosenfeld, Charles"; "Shankaran, Seetha"; "Stevenson, David"; "Stoll, Barbara"; "Tyson, Jon"; wrich@ucsd.edu
Subject:	Re: RE: DSMC
Date:	Saturday, March 04, 2006 12:23:07 AM

Great series of recomendations Michele
Why didn't I think of them?
It is critical for the wel being of the Nework that these issues be
resolved in an absolutely transparent manner
It is almost embarrasing that the Network has had so many miscues with
the DSMC and now is the time to fix them
Regards
Av

----- Original Message -----
From: Neil Finer <nfiner@ucsd.edu>
Date: Friday, March 3, 2006 7:35 pm
Subject: RE: DSMC
> Michele
> This is brilliant!!!!
> You rock!!
> Neil
>
> -----Original Message-----
> From: Michele Walsh [mailto:mcw3@case.edu]
> Sent: Friday, March 03, 2006 7:54 AM
> To: Fanaroff, Avroy; Carlo, Wally; Donovan, Edward (DONOVAEF); Duara,
> Shahnaz; Finer, Neil; Goldberg, Ron; Higgins, Rose; Jobe, Alan;
> Laptook,Abbot; Oh, William; Poole, Ken; Rosenfeld, Charles;
> Shankaran, Seetha;
> Stevenson, David; Stoll, Barbara; Tyson, Jon
> Subject: DSMC
>
> Hi All:
> I agree with Neil's comments and add the following.
> 1. The DSMC chair should be an active Neonatal clinician with
> knowledge of
> trials.
> 2. The DSMC charter should clearly spell out their mission and
> role in
> stopping trials.
> A training session may help to resolve some issues up front.
> 3. In person meetings have been shown to be more effective than
> conferencecalls. Costs can be minimized by having one DSMC meet
> with regularly
> scheduled meeting and oversight of all trials.
> 4. Investigators should define up front in protocol design
> possible adverse
> events and as was done in SUPPORT the expected variation in these
> outcomes.In addition, investigators in collaboration with
> statisticians should

> recommend the statistical techniques for spending the p value over
> multiplelooks. An independent statistician experienced in complex
> trial issues,
> such as Mark Klebanoff, should be a member of the DSMC in addition
> to the
> RTI statisticians.
> 5. Every meeting of the DSMC should begin with an open session
> where trial
> investigators can give the background of newly launched trials, or
> trials in
> design to receive the input of the committee and potentially
influence
> design. The investigators can educate the committee and give the
> benefit of
> the many hours of thought they have invested in the intervention
under
> study. DSMC than has a closed session.
> 6. Interim reports should be generated from 'cleaned data'. To
> ensurethis, PIs must have real time access to the data- even if
> this means a trip
> to RTI. Such cleaning will ultimately improve data validity and
trial
> integrity. Investigators should never see unmasked data, but
> should have
> input into the design of the analyses.
> 7. In factorial trials, only the arm with questions should be
> suspendedrather than the entire trial.
> 8. Members of the DSMC should sign confidentiality agreements and
> understand that if these are violated that they will be removed
> from the
> committee. I have heard too many "leaks" from third parties.
> I have found the following articles useful in learning more about the
> science of DSMCs. (See Attached. See Also: Thom and Klebanoff.
> Issues in
> clinical trial design: stopping a trial early and the large and
simpe
> trial. Am Journ OB&GYV. 2005; 193: 619-625)
> Since this is a relatively new area, I would propose that we
> write and
> submit a paper to a Clincal trials journal about these issues.
> Regards, Michele
>
>

From: Monica Konstantino
To: wrich@ucsd.edu
Cc: "Hastings, Betty J."; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: revised support forms
Date: Friday, March 03, 2006 12:19:58 PM

Wade Rich wrote:

>Monica,
>The check is not done live. The concept is that your nursing staff should,
>by current JCAHO monitoring standards, be checking those alarms anyway.
>The research staff just needs to see that it is documented and mark it as
>such. Your approach will work, but even that needs to be checked or
>documented to make sure it is still set. I guess the point is that we told
>the DSMC that we would make sure that the alarms were checked. How
>are you dealing with a baby who transiently goes into room air. Do they
>just have to deal with a high alarm, or are they able to disable it?
>wade
>
>-----Original Message-----
>From: Monica Konstantino [mailto:monica.konstantino@yale.edu]
>Sent: Friday, March 03, 2006 7:24 AM
>To: wrich@ucsd.edu
>Cc: betty
>Subject: revised support forms
>
>Hi Wade, in looking at the new forms and the documentation of the alarm
>settings we have used the home key on the oximeter so that the staff cannot
>change the alarms without a code that we set. This seems more practical
>then doing alarm checks every 6 hours 24/7, we don't think it would be
>possible to have the staff on the offshifts/weekends to remember to do these
>checks.
>Monica
>
>
>

We have only had the one baby on support who did very well and spent most of the time in RA but at first when she was only occasionally in RA then the staff would just listen to it (and drive them crazy) but once she was in RA for a long period of time we had to set the upper alarm to 100. We will have to educate the staff in future enrolled babies to document the settings at the specified times and see how that goes.
Monica

From:	Hastings, Betty J.
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; Auman, Jeanette O.; Poole, W. Kenneth; Zaterka-Baxter, Kristin; Gantz, Marie; Barbara.Alexander@cchmc.org; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD; Lenora Jackson
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Auman, Jeanette O.; Poole, W. Kenneth; Zaterka-Baxter, Kristin; Gantz, Marie; nfiner@ucsd.edu
Subject:	SUPPORT Forms
Date:	Tuesday, February 28, 2006 12:23:37 PM
Attachments:	SUPP11Rev[2-28-06] .doc SUPP05ASafetyMonitor2-28-06Rev.doc SUPP05SafetyMonitoRev2-28-06.doc

Attached please find the revised SUPPORT forms. Please note that the SUPP05 has been changed to allow for the recording of the FIO2 every 2 hours. In addition, the Intubation/Extubation is now a separate form (SUPP05A) and is to be used only as needed. The SUPP11 form has been revised to collect the additional data points, as well as the oximeter alarm check. Note: This form has been revised to collect down the form instead of across the form.

Please review these forms and send me your comments by Friday. Once these forms are final, the MOP will be revised and the updated versions will be sent to the sites.

Thanks for your help.
Betty <<SUPP11Rev[2-28-06] .doc>> <<SUPP05ASafetyMonitor2-28-06Rev.doc>> <<SUPP05SafetyMonitoRev2-28-06.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks __ __ / __ __ / __ __ __ __

Study Day	15 __ __/__ __/__ __ __ __ Month Day Year	16 __ __/__ __/__ __ __ __ Month Day Year	17 __ __/__ __/__ __ __ __ Month Day Year	18 __ __/__ __/__ __ __ __ Month Day Year	19 __ __/__ __/__ __ __ __ Month Day Year	20 __ __/__ __/__ __ __ __ Month Day Year
1. Scheduled Time: 06:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
2. Scheduled Time: 12:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
3. Scheduled Time: 18:00	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __
4. Scheduled Time: 23:59	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)	__ __ : __ __ (time measured)
(a) Highest Level of Support (Mode)	__	__	__	__	__	__
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.	__ __ . __ __ __ Liters/Min.
(d) Oximeter Alarm Check	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __	__ __ : __ __

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

This form should be completed if Question 15 on the SUPP05 was coded Yes.

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete Section C.

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 __ __ __

C. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 __ __ __

Initials of person completing this form: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP05 Rel 3.0
October 3, 2005
Revised February 28, 2006

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete a form each day through DOL 14

1. Study Day: __ __ 2. Date: __ __ / __ __ / __ __ __ __.

A. Record blood gas results, FiO_2 and Respiratory Support closest to the Scheduled Time. 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	(i) If Mode =5 record flow rate	***(j) If Mode =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __				__. __		__	__. __ __	__
2. 04 : 00	__ __ : __ __				__. __		__	__. __ __	__
3. 06 : 00	__ __ : __ __				__. __		__	__. __ __	__
4. 08 : 00	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	__	__	__. __ __	__
5. 10 : 00	__ __ : __ __				__. __		__	__. __ __	__
6. 12 : 00	__ __ : __ __				__. __		__	__. __ __	__
7. 14 : 00	__ __ : __ __				__. __		__	__. __ __	__
8. 16 : 00	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	__	__	__. __ __	__
9. 18 : 00	__ __ : __ __				__. __		__	__. __ __	__
10. 20 : 00	__ __ : __ __				__. __		__	__. __ __	__
11. 22 : 00	__ __ : __ __				__. __		__	__. __ __	__
12. 23 : 59	__ __ : __ __	__. __	__ __ __	__ __ __	__. __	__	__	__. __ __	__

13. Oximeter Alarm Check (record every 6 hours)

a. __ __ : __ __ (Hr Min) b. __ __ : __ __ (Hr Min) c. __ __ : __ __ (Hr Min) d. __ __ : __ __ (Hr Min)

14. Was a replacement study oximeter placed on this infant on this day? Y N

If Yes,

a. Serial number: __ __ __ __ __ __

*Source 1= Arterial 2= Venous 3 = Capillary

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

***CPAP Type 2= Ventilator 4= Bubble 6 = Flow Driver 9= Other

15. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

From: Betty Vohr
To: Higgins, Rosemary (NIH/NICHD) [E]; newman@rti.org; petrie@rti.org; poo@rti.org; adas@rti.org; edward.donovan@chmcc.org; mcw3@cwru.edu; nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; wrich@ucsd.edu; wcarlo@peds.uab.edu
Cc: joa@rti.org; schaefer@rti.org
Subject: RE: SUPPORT Follow Up
Date: Tuesday, February 28, 2006 10:09:40 AM

I would agree. The BITSEA is not a primary outcome.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 28, 2006 7:16 AM
To: newman@rti.org; petrie@rti.org; Betty Vohr; poo@rti.org; adas@rti.org; edward.donovan@chmcc.org; mcw3@cwru.edu; nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; wrich@ucsd.edu; wcarlo@peds.uab.edu
Cc: joa@rti.org; schaefer@rti.org
Subject: Re: SUPPORT Follow Up

We only need neurodeveleopmental outcome for the SUPPORT secondary outcome. I don't think we need the BITSEA.

Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Newman, Jamie <newman@rti.org>
To: Petrie, Carolyn <petrie@rti.org>; Betty Vohr <BVohr@WIHRI.org>; Poole, W. Kenneth <poo@rti.org>; Das, Abhik <adas@rti.org>; edward.donovan@chmcc.org <edward.donovan@chmcc.org>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; mcw3@cwru.edu <mcw3@cwru.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; reverett@med.miami.edu <reverett@med.miami.edu>; sduara@miami.edu <SDuara@miami.edu>; wrich@ucsd.edu <wrich@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>
CC: wrich@ucsd.edu <wrich@ucsd.edu>; Auman, Jeanette O. <joa@rti.org>; Schaefer, Scott E. <schaefer@rti.org>
Sent: Mon Feb 27 14:50:36 2006
Subject: RE: SUPPORT Follow Up

The NF13 (BITSEA) was not used for the babies greater than 1,000g (or for babies enrolled in non-Network centers) in the Preemie INO Study. Will we want to follow this precedent for the SUPPORT Follow-up?

Thanks, Jamie

Jamie E. Newman, MPH

Statistics and Epidemiology

RTI International

Telephone: (919) 485-5719

Fax: (919) 485-7762

newman@rti.org

From: Petrie, Carolyn
Sent: Monday, February 27, 2006 12:53 PM
To: Betty Vohr; Poole, W. Kenneth; Das, Abhik; edward.donovan@chmcc.org; higginsr@mail.nih.gov; Michele Walsh (mcw3@cwru.edu); nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; Wade Rich (wrich@ucsd.edu); wcarlo@peds.uab.edu
Cc: Newman, Jamie; 'Wade Rich (wrich@ucsd.edu)'; Auman, Jeanette O.; Petrie, Carolyn; Schaefer, Scott E.
Subject: SUPPORT Follow Up

We have Follow Up forms prepared for the 18 month visit for patients enrolled in SUPPORT, who are greater than 1000g and less than 401g.

It has been suggested that ALL follow up forms be completed on this subgroup. (Below is the list of the regular forms). We will rename them SF__ __ and they are ready to be installed in the data management system. I will send a memo to the group.

If you feel that we should not collect a particular form, please let use know so we can discuss the issue and give the appropriate instructions to the group. Thank you!!

NF00
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF00.pdf> Identification Information For Use with Base Record
NF01
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF01.pdf> SES at Discharge
NF02
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF02.pdf> Visit Log
NF03
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF03.pdf> SES at 18 + 4 Months
NF04
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Fo

rms/NF04.pdf> Medical History Form NF04A
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF04a.pdf> Readmission Form
NF05
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF05.pdf> Infant Examination Form NF05A
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF05A.pdf> Gross Motor Function Work Sheet
NF09
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF09.pdf> Bayley Scales Summary Score Sheet NF10
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF10.pdf> Status Form NF10A
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF10A.pdf> Status Form (NF10-A)
NF11
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF11.pdf> Summary of 18 Month Visit
NF12
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF12.pdf> Lost to Follow-up Questionnaire
NF13
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF13.pdf> BITSEA NF13S
<http://neonatal.rti.org/private/pdf/Protocols/Follow-up/18Month/2006/Forms/NF13S.pdf> BITSEA (Spanish)

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:	Betty Vohr
To:	Newman, Jamie; Petrie, Carolyn; Poole, W. Kenneth; Das, Abhik; 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:	wrich@ucsd.edu; Auman, Jeanette O.; Schaefer, Scott E.
Subject:	RE: SUPPORT Follow Up
Date:	Monday, February 27, 2006 7:16:49 PM

It would mean that the " standard neurodevelopmental" assessment would be done on all babies and the behavior assessment would be limited to infants < 1000 grams.

From: Newman, Jamie [mailto:newman@rti.org]
Sent: Monday, February 27, 2006 2:51 PM
To: Petrie, Carolyn; Betty Vohr; Poole, W. Kenneth; Das, Abhik; edward.donovan@chmcc.org; higginsr@mail.nih.gov; mcw3@cwru.edu; nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; wrich@ucsd.edu; wcarlo@peds.uab.edu
Cc: wrich@ucsd.edu; Auman, Jeanette O.; Schaefer, Scott E.
Subject: RE: SUPPORT Follow Up

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Thanks, Jamie

Jamie E. Newman, MPH
Statistics and Epidemiology
RTI International
Telephone: (919) 485-5719
Fax: (919) 485-7762
newman@rti.org

From: Petrie, Carolyn
Sent: Monday, February 27, 2006 12:53 PM
To: Betty Vohr; Poole, W. Kenneth; Das, Abhik; edward.donovan@chmcc.org; higginsr@mail.nih.gov; Michele Walsh (mcw3@cwru.edu); nfiner@ucsd.edu; reverett@med.miami.edu; sduara@miami.edu; Wade Rich (wrich@ucsd.edu); wcarlo@peds.uab.edu
Cc: Newman, Jamie; 'Wade Rich (wrich@ucsd.edu)'; Auman, Jeanette O.; Petrie, Carolyn; Schaefer, Scott E.
Subject: SUPPORT Follow Up

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It has been suggested that ALL follow up forms be completed on this subgroup. (Below is the list of the regular forms). We will rename them SF__ __ and they are ready to be installed in the data management system. I will send a memo to the group.

If you feel that we should not collect a particular form, please let use know so we can discuss the issue and give the appropriate instructions to the group. Thank you!!

NF00 Identification Information For Use with Base Record
NF01 SES at Discharge
NF02 Visit Log

NF03 SES at 18 + 4 Months
NF04 Medical History Form
NF04A Readmission Form
NF05 Infant Examination Form
NF05A Gross Motor Function Work Sheet
NF09 Bayley Scales Summary Score Sheet
NF10 Status Form
NF10A Status Form (NF10-A)
NF11 Summary of 18 Month Visit
NF12 Lost to Follow-up Questionnaire
NF13 BITSEA
NF13S BITSEA (Spanish)

Carolyn Petrie Huitema
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6110 Executive Blvd
Suite 902
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Wally Carlo, M.D.
To: nxs5@case.edu; Edward.Donovan@cchmc.org; mcw3@case.edu; mcw3@cwru.edu; Higgins, Rosemary (NIH/NICHD) [E]; sduara@miami.edu; bkh@rti.org; nfiner@ucsd.edu
Cc: nxs5@cwru.edu; adas@rti.org; kzaterka@rti.org; mgantz@rti.org; poo@rti.org; wrich@ucsd.edu; ahensman@wihri.org
Subject: Re: SUPPORT
Date: Friday, February 24, 2006 11:51:49 AM

Good idea.
Wally

-----Original Message-----
From: Nancy Newman <nxs5@case.edu>
To: 'Edward Donovan' <Edward.Donovan@cchmc.org>; 'Michele Walsh' <mcw3@case.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; 'Rosemary (NIH/NICHD) [E] Higgins' <higginsr@mail.nih.gov>; sduara@miami.edu <sduara@miami.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; 'Betty J. Hastings' <bkh@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>
CC: 'Nancy Newman' <nxs5@cwru.edu>; 'Abhik Das' <adas@rti.org>; 'Kristin Zaterka-Baxter' <kzaterka@rti.org>; 'Marie Gantz' <mgantz@rti.org>; 'W. Kenneth Poole' <poo@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; ahensman@wihri.org <ahensman@wihri.org>
Sent: Fri Feb 24 10:35:21 2006
Subject: RE: SUPPORT

I have one comment- we can reduce the mode of support collected on SUPP05- but we are collecting it 4 times/day on the SUPP11 which would be more often than 3 times a day with blood gases. Is the type of support and flow (if nasal cannula) important to correlate with the FiO2 and saturations??.....NN

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, February 24, 2006 10:16 AM
To: Michele Walsh; mcw3@cwru.edu; Rosemary (NIH/NICHD) [E] Higgins; sduara@miami.edu; wcarlo@peds.uab.edu; Betty J. Hastings; nfiner@ucsd.edu
Cc: Nancy Newman; Abhik Das; Kristin Zaterka-Baxter; Marie Gantz; W. Kenneth Poole; wrich@ucsd.edu; ahensman@wihri.org
Subject: Re: SUPPORT

agree with Michele about data volume

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> 02/24/2006 10:06:27 AM >>>

Hi All: I reviewed the forms. I agree with the changes.

I am concerned with the amount of data collected on Supp05- do we really need mode of support every two hours? How will we use this? It seems to me, that these fields could be blanked out and collected at the time points that blood gas data is collected.

Michele Walsh

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

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

To: Hastings, Betty J. <mailto:bkh@rti.org> ; nfiner@ucsd.edu ; mcw3@cwru.edu ; sduara@miami.edu ; wcarlo@peds.uab.edu ; edward.donovan@chmcc.org

Cc: Das, Abhik <mailto:adas@rti.org> ; Zaterka-Baxter, Kristin <mailto:kzaterka@rti.org> ; Poole, W. Kenneth <mailto:poo@rti.org> ; Gantz, Marie <mailto:mgantz@rti.org> ; ahensman@wihri.org ; Nancy Newman <mailto:nxs5@cwru.edu> ; wrich@ucsd.edu

Sent: Thursday, February 23, 2006 3:26 PM

Subject: RE: SUPPORT

If anyone has suggestions, please send them in ASAP (by tomorrow 5 PM at the latest) as some of the IRB s need the forms for final approval.

Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Wednesday, February 22, 2006 1:47 PM
To: nfiner@ucsd.edu; mcw3@cwru.edu; sduara@miami.edu; wcarlo@peds.uab.edu; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Poole, W. Kenneth; Gantz, Marie; ahensman@wihri.org; Nancy Newman; wrich@ucsd.edu
Subject: SUPPORT

Dear SUPPORT Subcommittee,
We (Nancy Newman, Angelita Hensman and Wade Rich) have been working on revising the forms in order to comply with the recommended changes that were presented to the DSMC. These are essentially to be able to record

the FIO2 every 2 hours and to have the oximeter alarm check recorded every 6 hours. Please review the three attached forms and provide us with feedback as soon as possible. Once these are approved by the Subcommittee, they will also be sent to the other coordinators for review. We would like to have these finalized just as soon as possible so the sites can submit them to their IRBs.

Thank you for you help.
Betty

<<SUPP11Rev[2-22-06] .doc>> <<SUPP05ASafetyMonitor2-22-06Rev.doc>> <<SUPP05SafetyMonitoRevr2-22-06.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
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: Neil Finer
To: "Hastings, Betty J."; mcw3@cwru.edu; sduara@miami.edu; wcarlo@peds.uab.edu; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Cc: "Das, Abhik"; "Zaterka-Baxter, Kristin"; "Poole, W. Kenneth"; "Gantz, Marie"; ahensman@wihri.org; "Nancy Newman"; wrich@ucsd.edu
Subject: RE: SUPPORT
Date: Friday, February 24, 2006 11:35:26 AM

Hi Everyone
I have reviewed the forms and discussed with Wade. The coordinators who put this together do not believe that the additional data being requested on SUPP 05 represents significant additional work. These forms were developed by them and I would support the forms as they have been written. If RTI feels that the including such data represents too much data then we can certainly go for only indicating the mode of vent support 3 times a day on SUPP 05

I have revised the Statement regarding Training for SUPPORT to reflect your input and we will not require a signed document from each site.
Let me know if you agree with this.
Neil

Subject: Statement re: Training for SUPPORT

The DSMC has accepted our recommendations regarding training of sites with respect to the maintenance of oxygen saturation within ranges. In order to integrate this into the trial, we would recommend the following information be included in an inservice at each site, and that the information provided be documented on the attached form.

1) That the concept of this portion of the trial is to create two groups of subjects with different oxygen exposures, and that in order for this to occur, the babies need to spend most of their time as close to 90% as possible.
2) The setting of alarms:
What levels we expect - 84-96 or tighter
When can they be disabled - Only when infant is in Room Air.

3) If Sat-Share is used, what does it do. -
Displays Masimo data on multiparameter monitor
Multi-parameter monitor uses own alarm and delay algorithms
4) What to do if baby is out of range.
Use Michelle's algorithm for weaning or increasing oxygen.

SUPPORT SATURATION RANGE

GOAL 88%-92% Broad Range 85-95%

IF BABY IS OUT OF RANGE

SaO_2 is	Wait	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	4-5%
<70	30 sec.	5%

5) Document that the SpO2 alarms are on and set properly - This will be data that we will collect on SUPP 05

In order for this process to be effective, the staff, including physicians, nurses, and therapists, need to commit to the process.

Sent: Wednesday, February 22, 2006 1:47 PM
To: nfiner@ucsd.edu; mcw3@cwru.edu; sduara@miami.edu; wcarlo@peds.uab.edu; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin; Poole, W. Kenneth; Gantz, Marie; ahensman@wihri.org; Nancy Newman; wrich@ucsd.edu
Subject: SUPPORT

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Thank you for you help.
Betty

<<SUPP11Rev[2-22-06] .doc>> <<SUPP05ASafetyMonitor2-22-06Rev.doc>> <<SUPP05SafetyMonitoRevr2-22-06.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]; Neil
Cc: Zaterka-Baxter, Kristin
Subject: SUPPORT
Date: Thursday, February 23, 2006 2:05:56 PM

Rose and Neil
We have sent in the IRB amendment as an FYI at our site. I note the memo of Feb 9 from RTI (technical memo) talks about 8 points that do involve change. Should we go ahead with screening or await IRB response since the 8 points do appear in the minutes that we all just submitted to the IRB
Thanks much
Seetha

From:	Hastings, Betty J.
To:	nfiner@ucsd.edu; mcw3@cwru.edu; sduara@miami.edu; wcarlo@peds.uab.edu; edward.donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Das, Abhik; Zaterka-Baxter, Kristin; Poole, W. Kenneth; Gantz, Marie; ahensman@wihri.org; Nancy Newman; wrich@ucsd.edu
Subject:	SUPPORT
Date:	Wednesday, February 22, 2006 2:07:40 PM
Attachments:	SUPP11Rev[2-22-06] .doc SUPP05ASafetyMonitor2-22-06Rev.doc SUPP05SafetyMonitoRevr2-22-06.doc

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Dear SUPPORT Subcommittee,

We (Nancy Newman, Angelita Hensman and Wade Rich) have been working on revising the forms in order to comply with the recommended changes that were presented to the DSMC. These are essentially to be able to record the FIO2 every 2 hours and to have the oximeter alarm check recorded every 6 hours. Please review the three attached forms and provide us with feedback as soon as possible. Once these are approved by the Subcommittee, they will also be sent to the other coordinators for review. We would like to have these finalized just as soon as possible so the sites can submit them to their IRBs.

Thank you for you help.
Betty

<<SUPP11Rev[2-22-06] .doc>> <<SUPP05ASafetyMonitor2-22-06Rev.doc>>
<<SUPP05SafetyMonitoRevr2-22-06.doc>>

Betty Hastings

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Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

RESPIRATORY SUPPORT AFTER 14 DAYS

Center: ___ Site No: ___ Network No: _____ Birth No: ___ Mother's Initials: _____

Complete this form daily from study day 15 through 36 weeks or status, whichever comes first.

Date of 36 weeks ___/___/_____

Study Day	15 ___/___/_____ Month Day Year	16 ___/___/_____ Month Day Year	17 ___/___/_____ Month Day Year	18 ___/___/_____ Month Day Year	19 ___/___/_____ Month Day Year	20 ___/___/_____ Month Day Year
1. Scheduled Time: 06:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
2. Scheduled Time: 12:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
3. Scheduled Time: 18:00	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___
4. Scheduled Time: 23:59	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)	___:___ (time measured)
(a) Highest Level of Support (Mode)	___	___	___	___	___	___
(b) Oxygen	YES NO	YES NO	YES NO	YES NO	YES NO	YES NO
(c) Flow Rate (NC only)	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.	___.___ Liters/Min.
(d) Oximeter Alarm Check	___:___	___:___	___:___	___:___	___:___	___:___

****Mode** 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM (Supplemental Form)

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __ Report No. __ __

This form should be completed if Question 15 on the SUPP05 was coded Yes.

1. Study Day: __ __ **2. Date:** __ __ / __ __ / __ __ __ __

B. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY) If more than one intubation/extubation occurs in one day, complete Section C.

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 __ __ __

C. INTUBATED/EXTUBATED INFORMATION (FOR NICU ONLY)

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 __ __ __

Initials of person completing this form: __ __ __

NICU Network

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

SAFETY MONITORING FORM

SUPP 05 Rel 3.0
October 3, 2005
Revised February 21, 2006

Center: __ __ Site No: __ Network No: __ __ __ __ Birth No: __ Mother's Initials: __ __ __

Complete a form each day through DOL 14

1. Study Day: __ __ 2. Date: __ __ / __ __ / __ __ __ __.

A. Record blood gas results, FiO_2 and Respiratory Support closest to the Scheduled Time. 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	(i) Flow Rate	***(j) If Mode of Support =4 (CPAP) Type used
1. 02 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
2. 04 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
3. 06 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
4. 08 : 00	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___	__ . __ __ __	___
5. 10 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
6. 12 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
7. 14 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
8. 16 : 00	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___	__ . __ __ __	___
9. 18 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
10. 20 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
11. 22 : 00	__ __ : __ __				__ . __ __		___	__ . __ __ __	___
12. 23 : 59	__ __ : __ __	__ . __ __	__ __ __	__ __ __	__ . __ __	___	___	__ . __ __ __	___

*Source 1= Arterial 2= Venous 3 = Capillary

**Mode 1= HFV 2= CV 3= Nasal SIMV 4= CPAP 5= NC 6=Hood 7= No Support

***CPAP Type 2= Ventilator 4= Bubble 6 = Flow Driver 9= Other

13. Oximeter Alarm Check (record every 6 hours)

a. __ __ : __ __ Hr Min b. __ __ : __ __ Hr Min c. __ __ : __ __ Hr Min d. __ __ : __ __ Hr Min

14. Was a replacement study oximeter placed on this infant on this day? Y N

If Yes,

a. Serial number: __ __ __ __ __ __

15. Was the Infant intubated or extubated on this day? Y N

If Yes, complete the SUPP05A

Initials of person completing this form: __ __ __

From: Michele Walsh
To: Neil Finer; "Wally Carlo, M.D."
Cc: "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"
Subject: Re: Statement re: Training for SUPPORT
Date: Wednesday, February 22, 2006 12:08:59 PM

Sounds ok to me. Michele

----- Original Message -----
From: Neil Finer
To: 'Wally Carlo, M.D.'
Cc: 'Avroy A. Fanaroff, M.D.' ; 'Betty Hastings' ; Das, Abhik ; 'Ed Donovan' ; higginsr@mail.nih.gov ; 'Ken Poole' ; 'Maynard Rasmussen' ; 'Michele' ; 'Neil Finer' ; 'Shahnaz Duara' ; 'Wade Rich'
Sent: Tuesday, February 21, 2006 10:46 PM
Subject: RE: Statement re: Training for SUPPORT

Hi Wally
I had removed the references to the asterisks and forgot to remove the asterisks. I removed these because each unit may use different values and SatShare will change this as well. Let me know if this is OK
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, February 21, 2006 7:23 PM
To: Neil Finer; Avroy A. Fanaroff, M.D.; Betty Hastings; Das, Abhik; Ed Donovan; higginsr@mail.nih.gov; Ken Poole; Maynard Rasmussen; Michele; Shahnaz Duara; Wade Rich
Subject: RE: Statement re: Training for SUPPORT

I think we should clarify what the asterisks mean. As I understood from Michele, it is that ~30 sec delay of the instrument is included in this delay in response so by the time the alarm goes off with SpO2 <70, it is time to increase FiO2 not wait 30 sec more.

Is that correct? We should explain in the text what the asteriks mean. wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, February 21, 2006 10:34 AM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; Das, Abhik; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; Wally Carlo, M.D.
Subject: FW: Statement re: Training for SUPPORT

Hello Everyone
Please review the statements below and let me know if you are in agreement.
I think that it is essential to lay out our proposed action plan.
Thanks
Neil

Subject: Statement re: Training for SUPPORT

The DSMC has accepted our recommendations regarding training of sites with respect to the maintenance of oxygen saturation within ranges. In order to integrate this into the trial, we would recommend the following information be included in an inservice at each site, and that the information provided be documented on the attached form.

1) That the concept of this portion of the trial is to create

two groups of subjects with different oxygen exposures, and that in order for this to occur, the babies need to spend most of their time as close to 90% as possible.

2) The setting of alarms:
   What levels we expect - 84-96 or tighter
   When can they be disabled - Only when infant is in Room Air.

3) If Sat-Share is used, what does it do. -
   Displays Masimo data on multiparameter monitor
   Multi-parameter monitor uses own alarm and delay algorithms

4) What to do if baby is out of range.
   Use Michelle's algorithm for weaning or increasing oxygen.

SUPPORT SATURATION RANGE

GOAL 88%-92% Broad Range 85-95%

IF BABY IS OUT OF RANGE

SaO_2 is	Wait**	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	4-5%
<70	30 sec.	5%

5) Document that the SpO2 alarms are on and set properly - This will be data that we will collect on SUPP 05

In order for this process to be effective, the staff, including physicians, nurses, and therapists, need to commit to the process. We would suggest that a simple document like the one attached be signed and sent from the PI to RTI indicating that the site has provided this training, intends to continue to integrate the training into their inservice schedule, and that the medical staff agrees with the tenets included in the training.

From:	Wally Carlo, M.D.
To:	Edward Donovan; Higgins, Rosemary (NIH/NICHD) [E]; Shahnaz Duara; M.D." "Avroy A. Fanaroff; Michele; Abhik Das; Betty Hastings; Ken Poole; Maynard Rasmussen; Neil Finer; Wade Rich
Subject:	RE: Statement re: Training for SUPPORT
Date:	Wednesday, February 22, 2006 8:00:59 AM

Neil: I agree with Ed about the signature. Wally

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, February 22, 2006 6:29 AM
To: higginsr@mail.nih.gov; 'Shahnaz Duara'; Wally Carlo, M.D.; M.D.' 'Avroy A. Fanaroff; 'Michele'; Abhik Das; 'Betty Hastings'; 'Ken Poole'; 'Maynard Rasmussen'; Neil Finer; 'Wade Rich'
Subject: FW: Statement re: Training for SUPPORT

Neil.
Looks fine. I agree with Wally - not sure what the asterisks mean.
Not sure that agree with asking Coord. and PI to sign - I think we should state clearly that, unless otherwise stated, we will assume that Coord and PI are in agreement.
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 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Neil Finer" <nfiner@ucsd.edu> 02/21/2006 11:33:38 AM >>>

Hello Everyone
Please review the statements below and let me know if you are in agreement. I think that it is essential to lay out our proposed action plan.
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Neil

Subject: Statement re: Training for SUPPORT

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SUPPORT SATURATION RANGE

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<70	30 sec.	5%

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From: Petrie, Carolyn
To: Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; bvohr@wihri.org
Cc: wrich@ucsd.edu; Petrie, Carolyn
Subject: RE: SUPPORT Follow Up
Date: Tuesday, February 21, 2006 1:25:45 PM

Hi all-

It has been suggested that for kids less than 400g and greater than 1001g we should only collect data on the following forms:

NF00 Identification Information For Use with Base Record
NF02 Visit Log
NF03 SES at 18 + 4 Months
NF04 Medical History Form
NF04A Readmission Form
NF05 Infant Examination Form
NF05A Gross Motor Function Work Sheet
NF09 Bayley Scales Summary Score Sheet
NF10 Status Form
NF10A Status Form (NF10-A)
NF11 Summary of 18 Month Visit
NF12 Lost to Follow-up Questionnaire

Don't need NF01 because this looks for a change in SES data, is this pertinent to the study
Don't' need NF13 will this information be used in the SUPPORT study
Don't need the NF14, phototherapy study.

NF01 SES at Discharge
NF13 BITSEA
NF13S BITSEA (Spanish)
NF14 Hearing Assessment Form

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, February 21, 2006 11:35 AM
To: Petrie, Carolyn; 'Higgins, Rosemary (NIH/NICHD) [E]'; bvohr@wihri.org
Cc: wrich@ucsd.edu
Subject: RE: SUPPORT Follow Up

Hi Carolyn
These infant need the same follow-up as the infants < 1000 gm
Thanks
Neil

From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tuesday, February 21, 2006 7:34 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; bvohr@wihri.org

Subject: SUPPORT Follow Up

Hi-

At point very soon, we need to look at the kids who are greater than 1000g and seen at follow up.

Ie, do we need to ask all the questions.

I must send an email to the group, asking them to hold onto SES at discharge forms until we get the system up and running to handle kids over 1000g.

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:	Betty Vohr
To:	Neil Finer; Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	wrich@ucsd.edu
Subject:	RE: SUPPORT Follow Up
Date:	Tuesday, February 21, 2006 11:49:14 AM

Right. If they are enrolled in the Support study they will need to follow the exact follow-up protocol.

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, February 21, 2006 11:35 AM
To: 'Petrie, Carolyn'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Betty Vohr
Cc: wrich@ucsd.edu
Subject: RE: SUPPORT Follow Up

Hi Carolyn
These infant need the same follow-up as the infants < 1000 gm
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From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Tuesday, February 21, 2006 7:34 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; bvohr@wihri.org
Subject: SUPPORT Follow Up

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Rockville, MD 20852
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fx. (301) 230-4646

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"
Subject: FW: Statement re: Training for SUPPORT
Date: Tuesday, February 21, 2006 11:37:31 AM
Attachments: February 17th.doc

Hello Everyone
Please review the statements below and let me know if you are in agreement. I think that it is essential to lay out our proposed action plan.
Thanks
Neil

Subject: Statement re: Training for SUPPORT

The DSMC has accepted our recommendations regarding training of sites with respect to the maintenance of oxygen saturation within ranges. In order to integrate this into the trial, we would recommend the following information be included in an inservice at each site, and that the information provided be documented on the attached form.

1) That the concept of this portion of the trial is to create two groups of subjects with different oxygen exposures, and that in order for this to occur, the babies need to spend most of their time as close to 90% as possible.
2) The setting of alarms:
   What levels we expect - 84-96 or tighter
   When can they be disabled - Only when infant is in Room Air.

3) If Sat-Share is used, what does it do. -
   Displays Masimo data on multiparameter monitor
   Multi-parameter monitor uses own alarm and delay algorithms
4) What to do if baby is out of range.
   Use Michelle's algorithm for weaning or increasing oxygen.

SUPPORT SATURATION RANGE

GOAL 88%-92% Broad Range 85-95%

IF BABY IS OUT OF RANGE

SaO_2 is	Wait**	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	4-5%
<70	30 sec.	5%

5) Document that the SpO2 alarms are on and set properly - This will be data that we will collect on SUPP 05

In order for this process to be effective, the staff, including physicians, nurses, and therapists, need to commit to the process. We would suggest that a simple document like the one attached be signed and sent from the PI to RTI indicating that the site has provided this training, intends to continue to integrate the training into their inservice schedule, and that the medical staff agrees with the tenets included in the training.

February 17th, 2006

To: RTI

From: Dr. X
Site ##
NICHD Neonatal Network

Re: Support Training

The medical staff at our site has agreed to abide by the guidelines provided in the SUPPORT Oxygen Training powerpoint presentation, and has provided this training to the NICU staff. We also understand that a continuous commitment to this training will be necessary to insure that new staff understands how oxygen will be managed in our SUPPORT infants.

_____ _____

Principal Investigator Coordinator

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CLINICAL TRIALS . GOV
Date: Tuesday, February 21, 2006 11:00:25 PM

Thanks Rose
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 21, 2006 3:21 PM
To: nfiner@ucsd.edu
Cc: wrich@ucsd.edu
Subject: Re: SUPPORT CLINICAL TRIALS . GOV

Thanks - that looks fine. The re-start date was Feb 6- I will add it and get it posted tomorrow!

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: wrich@ucsd.edu <wrich@ucsd.edu>
Sent: Tue Feb 21 17:58:39 2006
Subject: RE: SUPPORT CLINICAL TRIALS . GOV

I think that this looks fine - I have added a brief phrase below.

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 21, 2006 11:30 AM
To: Neil Finer
Subject: SUPPORT CLINICAL TRIALS . GOV

Neil

WE need to post something on the clinicaltrials.gov website for the SUPPORT Trial. This can be accessed by anyone including parents so we toned the language to consider the audience. I will get the official re-start date from Betty - does this looks ok to you? Also, if there are other investigators in need of the DSMC information, we could send it to them confidentially (as opposed to putting more detail on the clinicaltrials.gov website).

The SUPPORT Trial recruitment was temporarily paused based on concern regarding pulse oximeter readings > 95% and due to concern regarding separation of the two arms of the oximetry portion of the study. Further analyses were performed which showed that infants on room air accounted for a significant portion of pulse oximetry saturations above 95%. Separation of the two groups was reanalyzed based on time spent in room air and the duration of time spent at individual SpO2 values, which both showed group differences. The trial was restarted on___ (date).

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: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Hastings, Betty J.
Subject: FW: Support Re-activation
Date: Tuesday, February 21, 2006 10:49:32 AM

Hi Rose,
Please see Miami's email below re- the Support re-activation; didn't know if I could send it to Neil yet. Do you know if this also means the Growth Secondary will not move forward?
Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Everett, Ruth [mailto:REverett@med.miami.edu]
Sent: Tuesday, February 21, 2006 10:09 AM
To: Zaterka-Baxter, Kristin
Subject: RE: Support Re-activation

Hi Kristin, unfortunately Miami will not be part of the network and therefore will not seek approval for reactivation, and as of March 31, we will no longer be enrolling in any studies and I will close all studies for the NICHD except follow-up, extended follow-up, and breathing outcomes, or any study that has a follow-up component.

> -----Original Message-----
> **From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
> **Sent:** Monday, February 20, 2006 10:27 AM
> **To:** Everett, Ruth; auten002@mc.duke.edu; mcollins@peds.uab.edu
> **Subject:** FW: Support Re-activation
>
> Hi all,
> When you have a second, would you please let me know your IRB status for the re-activation of Support. I apologies if you've already sent this but I unfortunately do not have a record.
> Thanks,
> Kris

> **From:** Zaterka-Baxter, Kristin
> **Sent:** Friday, February 17, 2006 12:47 PM
> **To:** 'Angelita Hensman (ahensman@wihri.org)'; 'mbball@leland.stanford.edu'; 'Cathy Grisby (grisbyca@email.uc.edu)'; 'ellen_hale@oz.ped.emory.edu'; 'Gay Hensley (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 (monica.konstantino@yale.edu)'; 'Nancy Miller (Nancy.Miller@UTSouthwestern.edu)'; 'Nancy Newman'; 'npeters@wfubmc.edu'; 'Rebecca Bara (ae5357@wayne.edu)'; 'Risa Demetrio (risa.demetrio@sharp.com)'; 'RN Judy Hall (jyhall@stanford.edu)'; 'kathy.arnell@sharp.com'; 'Ruth Everett (Reverett@med.miami.edu)'; 'Wade Rich (wrich@ucsd.edu)'; 'Charles Rosenfeld MD (charles.rosenfeld@utsouthwestern.edu)';

'M. D. Abbot Laptook (alaptook@wihri.org)'; 'Jobea0@chmcc.org'; 'aaf2@po.cwru.edu'; [SCRN] Stoll, Barbara; 'bpoindex@iupui.edu'; 'dale_phelps@urmc.rochester.edu'; 'dstevenson@stanford.edu'; 'edward.donovan@chmcc.org'; 'jlemons@iupui.edu'; 'jon.e.tyson@uth.tmc.edu'; 'moshea@wfubmc.edu'; 'nfiner@ucsd.edu'; 'richard.ehrenkranz@yale.edu'; 'M. D. Ronald Goldberg (goldb008@mc.duke.edu)'; 'M. D. Seetha Shankaran (sshankar@med.wayne.edu)'; 'sduara@miami.edu'; 'wcarlo@peds.uab.edu'; 'M. D. William Oh (woh@wihri.org)'; 'M. D. Michele Walsh (mcw3@cwru.edu)'; ' (Walid.Salhab@UTSouthwestern.edu)'; 'Barbara Alexander (Barbara.Alexander@cchmc.org)'; 'Lenora Jackson'; 'Estelle E. Fischer'; 'Holly Mincey'; 'Jody Shively'; 'Kate Bridges, MD'
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Hastings, Betty J.; 'Phelps, Dale'; Newman, Jamie
Subject: Support Re-activation

Hi all,
We have a quick follow up questions from the coordinators conference call yesterday regarding site IRB approvals for re-activation of the Support trial.
How many sites have obtained re-activation approval, how many sites have submitted and are waiting for approval and how many have not started the IRB submission process. Please send me a quick email with your sites status.
Very much appreciated as always,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
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Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From:	Wally Carlo, M.D.
To:	Duara, Shahnaz; nfiner@ucsd.edu; mcw3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]; Edward.Donovan@cchmc.org; wrich@ucsd.edu; Nxs5@po.cwru.edu
Cc:	Wally Carlo, M.D.
Subject:	RE: Updated DSMC slides
Date:	Wednesday, January 18, 2006 11:28:19 AM
Attachments:	DSMC Jan 17 revised.ppt

Dear all:
I have made the following changes directly to the slides.

Slide #4: Under bullet 2 - made the "o" in oxygen lowercase. Bullet 3 - changed the word "significantly" to "markedly".

Slide # 8: In the 4th bullet, first line - changed "this" to "these" data. . . .

Slide #12: Changed the bullets from "x" to "*". Moved (Ng et al Arch Dis Child 1998;79:F64) to second level bullet position.

Slide #13: Added the subtitle "Percent of Time Spent at SPO2 > 96%". Moved the paragraph "Infants in room air.... to the end of the page".

Slide # 21: Added the subtitle: Summary - 1

Slide #22: Added the subtitle: Summary 3. Deleted the word "to" in the first line. Added a bullet at the end that reads: "Similar small studies report a higher percent of SaO2 > 95% than in the high target group in SUPPORT.

Slide #32: Aligned paragraphs on the left.

Slide #33: Added "s" to Conclusion

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 24, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became markedly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by > 9% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- **The optimal saturation range for ELBW is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Evidence for Currently used SpO2 Ranges is Lacking

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.**

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting these data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- **14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks**
- **Study performed to document practice prior to a trial with design parallel to SUPPORT**
- **Reported SpO2 limits ranged:**
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- **Median SpO2 in Hagadorn = 95%**
- **Median SpO2 from SUPPORT –**
  - All infants in trial = 92% and 94%
  - Infants in Oxygen = 91% and 93%
- **Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.**

Additional Evidence

Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%

- **Hagadorn study-**
  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants-**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW non-SUPPORT 51% time SpO2 > 95%**

Effects of Room Air on SpO2 > 95%

- **SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time**
- **The Median SpO2 values while in Room air for the 91%-95% and 85%-89% Groups are 97% and 96%**
- **Median SpO2 in healthy preterm infants in room air = 97%**
  - (Ng et al Arch Dis Child 1998;79:F64)
- **Infants in room air can not have changes made to their inspired oxygen to lower their SpO2s.**

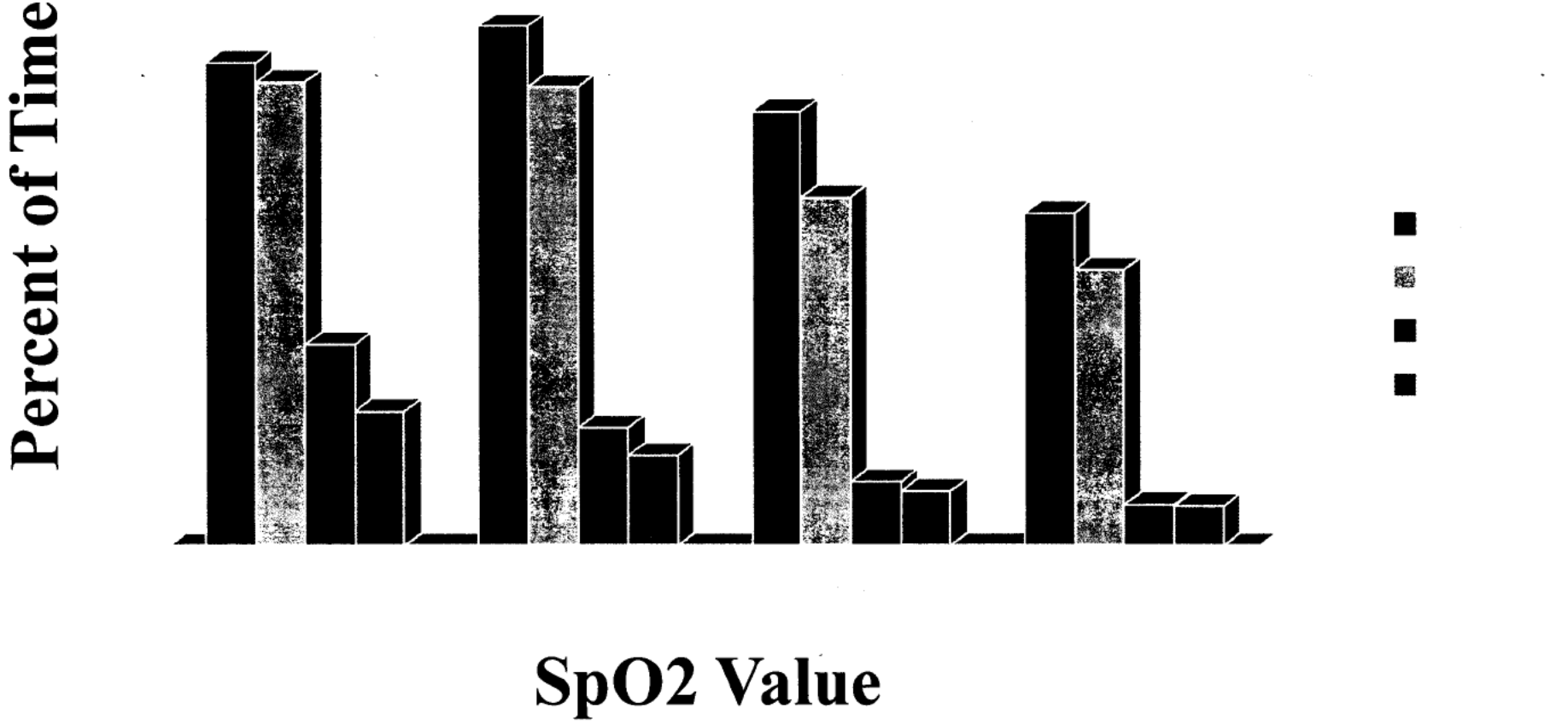
SpO2 values of SUPPORT infants in Room Air

Percent of Time Spent at SpO_2 > 96^

	91%- 95% Group	85% - 89% Group
Room Air	52.7%	46.1%
Oxygen	12.6%	9.4%

- Infants in room air had a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



The Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **These files can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Evaluation of SpO2 Information

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Evaluation of SpO2 ranges

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%
- Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.
- This incorrectly assigned some infants in RA to the Oxygen analysis.

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95%
Summary - 1

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to greater durations of SpO2 > 95% while receiving oxygen than ELBW infants currently receiving usual care.**
- **Previous analyses overstated the exposure.**
- **Most of the overestimate was from misclassification of infants in partial oxygen.**

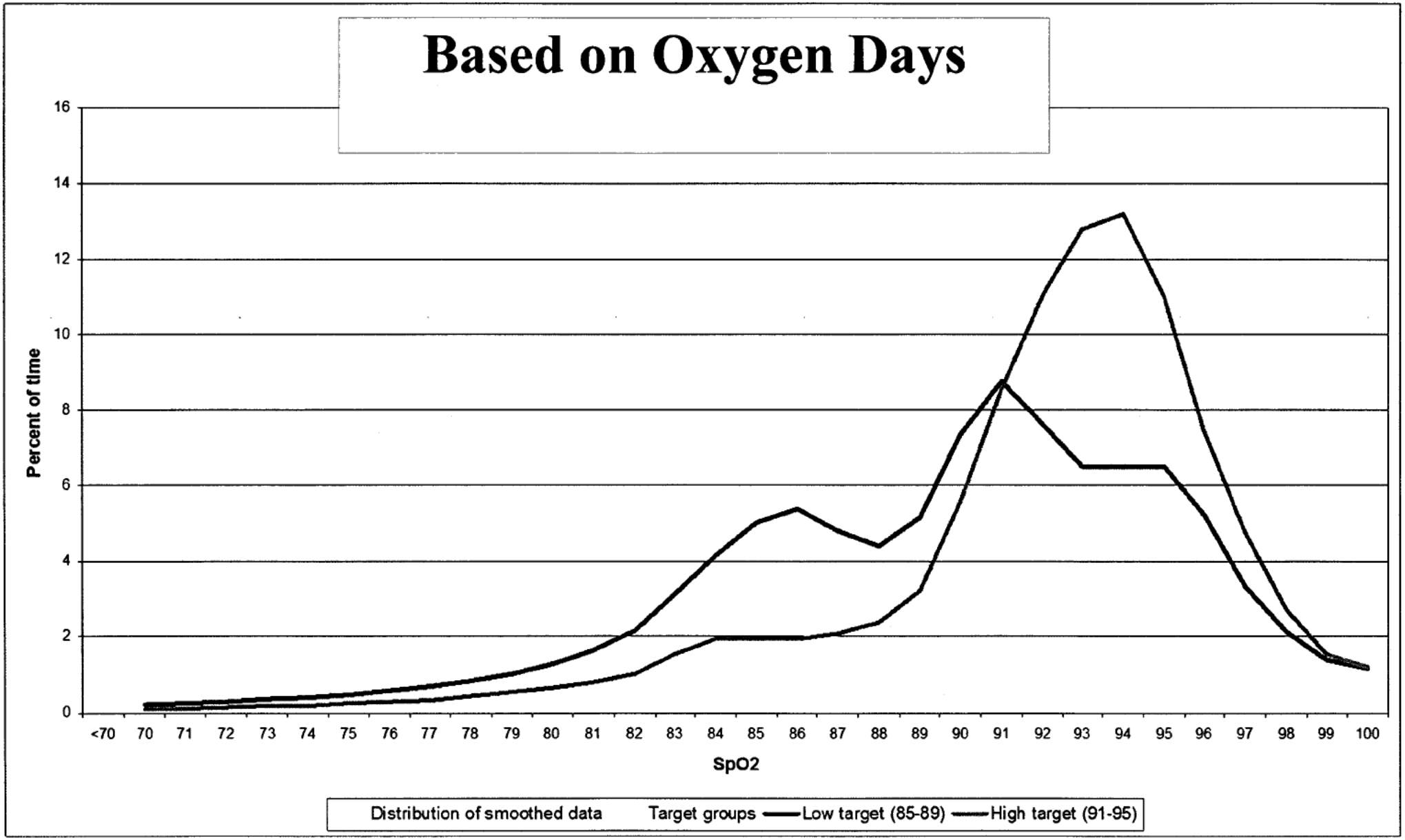
Safety Issue of SpO2 > 95% Summary - 2

- This trial will help determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.
- Similar small studies report a higher present of SaO_2 > 95% than in the high target group in SUPPORT

Futility Regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - **Mean all infants – 90% vs 92%**
  - **Median all infants – 92% vs 94%**
  - **Median infants in oxygen at all 3 data points - 91% vs 93%**
- **Time with an SpO2 of ≤90% shows a difference of > 24%**
  - **91% - 95% Group = 22.8%**
  - **85% - 89% Group = 47.6%**

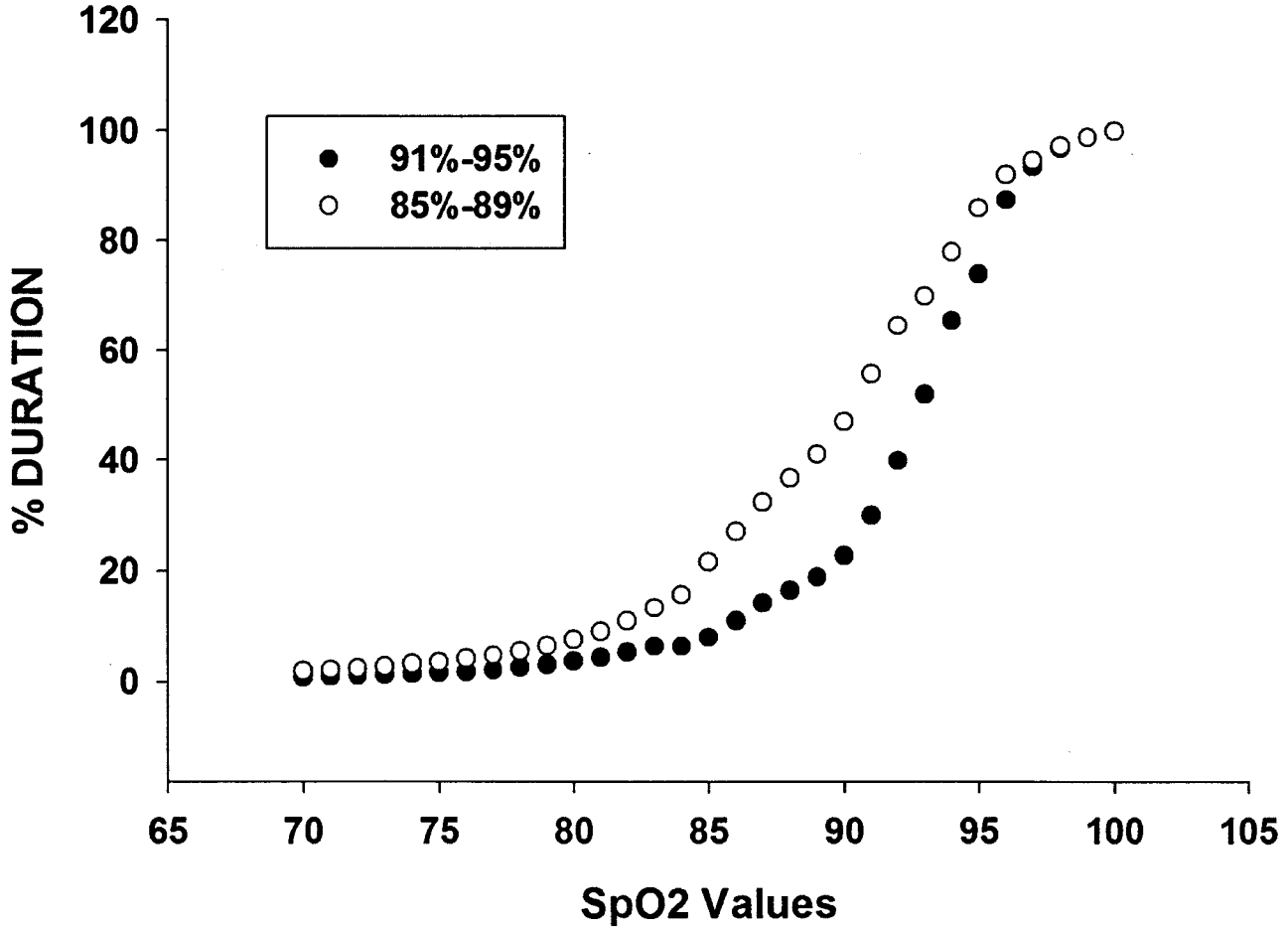
P9



Slide 24

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



5-04582

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 requirements between the groups**

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - **91%-95% group = 26.6%**
  - **85%-89% group = 35.5%**
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

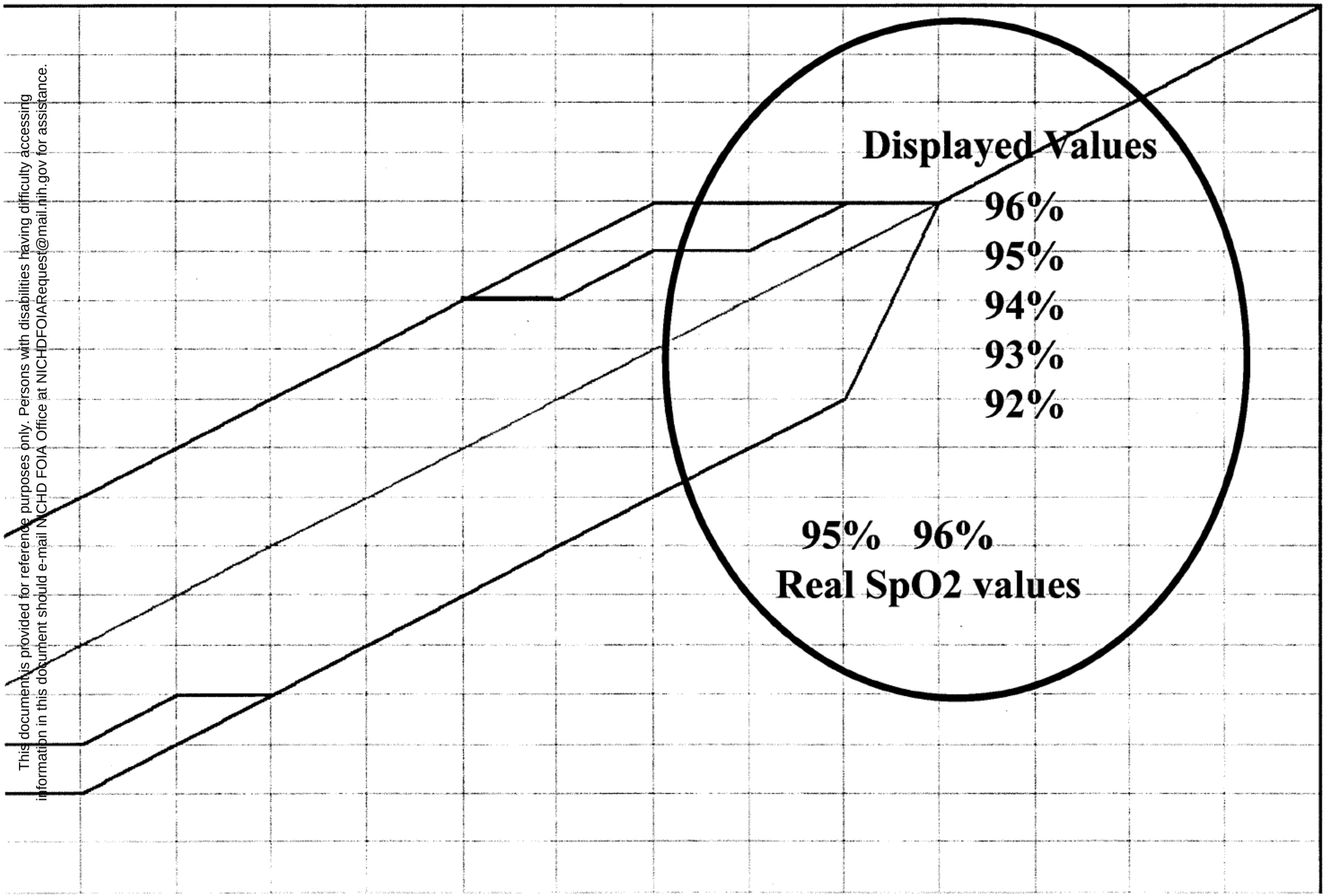
7. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**
8. **Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.**

Conclusions

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

SpO2 Algorithm

- **These SpO2 values represent an overlap of altered and real values of the SUPPORT SpO2 algorithm**
- **All displayed SpO2 values in SUPPORT > 96% and < 84% represent the actual unaltered SpO2**
- **Therefore, subsequent data will be presented for values > 96% and < 84%, rather than the expected >95% and <85%**



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; charles.rosenfeld@utsouthwestern.edu; alaptook@wihri.org; Jobea0@chmcc.org; aaf2@po.cwru.edu; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; dstevenson@stanford.edu; edward.donovan@chmcc.org; 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; Barbara.Alexander@cchmc.org; Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD

Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Phelps, Dale; Newman, Jamie

Subject: Support Re-activation

Date: Friday, February 17, 2006 12:47:24 PM

Hi all,

We have a quick follow up questions from the coordinators conference call yesterday regarding site IRB approvals for re-activation of the Support trial.

How many sites have obtained re-activation approval, how many sites have submitted and are waiting for approval and how many have not started the IRB submission process. Please send me a quick email with your sites status.

Very much appreciated as always,

Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer
To: "Michele Walsh"
Cc: "Wade"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, February 16, 2006 6:32:14 PM

Thanks Michele
We will incorporate these into our guidelines. Have you tested these guidelines with respect to showing more time in target compared to SOC?
Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Thursday, February 16, 2006 1:52 PM
To: nfiner@ucsd.edu
Cc: Higgins, Rose
Subject: Re: SUPPORT

revisions attached. We are planning on opening the sat window and adjusting how we respond. Michele

----- Original Message -----
From: Neil Finer
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: wrich@ucsd.edu ; 'Michele Walsh'
Sent: Thursday, February 16, 2006 3:51 PM
Subject: RE: SUPPORT

Hi Rose
Absolutely. Also we should ask if there are issues that we could help with.
In addition, I think that we should try to get the additional FiO2 data – ie q2h for the first 14 days and then q4h after 14 days if on Oxygen or support of any kind. Our site would have the most work to do. In addition as almost ¼ of the infants have been enrolled, this information will allow a better matching of oxygen use with oximetry results.
I will call Michele today (I have already tried) to find out when we can expect to get the oxygen guidelines that she is revising.
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 16, 2006 8:41 AM
To: Neil Finer
Subject: SUPPORT

Neil
I spoke to Seetha this am and they are screening now for SUPPORT. Their IRB has given them the go-ahead to restart. Would you like us to poll the network to see where folks are with re-approval? It may give some added push to get going.

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

From: Michele Walsh
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Thursday, February 16, 2006 4:54:02 PM
Attachments: SUPPORT SATURATION RANGEGOAL 88%92%IF BABY IS OUT OF RANGEmw edit.rtf

---

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----- Original Message -----
From: Neil Finer
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: wrich@ucsd.edu ; 'Michele Walsh'
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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

SUPPORT SATURATION RANGE

GOAL 88%-92%85-95%

IF BABY IS OUT OF RANGE

SaO_2 is	Wait**	Adjust FiO_2 by
80-85 or 95-99	1 min.	2%
70-80 or 100	1 min.	4-5%
<70	30 sec.	5%

**Remember, there is a 30 sec. delay in the readout of the monitor

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Thursday, February 16, 2006 4:19:04 PM

Sure.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 16, 2006 3:53 PM
To: Hastings, Betty J.
Subject: FW: SUPPORT

FYI

can you find out which sites are ready to go from the irb standpoint?

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, February 16, 2006 3:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: wrich@ucsd.edu; 'Michele Walsh'
Subject: RE: SUPPORT

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In addition, I think that we should try to get the additional FiO2 data – ie q2h for the first 14 days and then q4h after 14 days if on Oxygen or support of any kind. Our site would have the most work to do. In addition as almost ¼ of the infants have been enrolled, this information will allow a better matching of oxygen use with oximetry results.
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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: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Wade"
Subject: RE:
Date: Monday, February 13, 2006 3:26:44 PM

Hi Rose
I tried to call you and will try again later. I have an additional question. If our site could get funding for patient enrollment for SUPPORT from Masimo, (I have not asked them at this time), would we be allowed to continue to enroll as part of the trial and send data to RTI etc? I know we have no agreement with them but a clinical trials agreement between Masimo and UCSD could be structured, or with the NICHD - whatever was preferred.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 13, 2006 7:42 AM
To: Neil Finer
Subject: RE:

http://www.grants.nih.gov/grants/guide/notice-files/not97-232.html

Neil,
Thanks for taking the time to speak with me. The above link describes appeal processes for scientific review of applications. Let me know if you have any questions that I can assist in answering.
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Saturday, February 11, 2006 9:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Wade'; Gabriel Haddad
Subject:

Hello Rose
We at UCSD have given a great deal of thought to the news that we did not successfully recompete in the NRN
We have reviewed the critiques that we were sent. We are concerned that the third reviewer's critique which made no specific comments about the contents of the grant, and which made (b) (5) (b) (5) may have resulted in our poor score.
We were careful to state in the grant that we had designed, led and completed DR-CPAP and then followed with SUPPORT. We included our detailed design about the oximeter algorithm which is being used by virtually every other trial in the Australia, England and Canada and in the US if Cindy Cole is funded.
Other senior members of our University Administration are also concerned at the inconsistency of the reviews.
I would like to know if we could obtain any more detailed critique so that we could better understand the decision and score.
We have been totally committed to the Neonatal Network, and this has continued up to the present with my presentation to the DSMC to defend the trials and ensure its continuation.
Other senior NRN members have also indicated their surprise and concern at the decision that we are no longer members.
Was there a program officer present during the review who could share with use any additional

information?
We remain puzzled, concerned and committed.
In addition can you advise how we would best proceed to appeal this decision.
I hope that you can shed some light on this issue for us.
Many thanks
Neil

From: Petrie, Carolyn
To: Petrie, Carolyn; Poole, W. Kenneth; 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: diane.timmer@cchmc.org; fmartinez@ucsd.edu; cdg2749@yahoo.com; aellison@med.miami.edu; msumner@peds.uab.edu; Gantz, Marie; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT--Ancillary: Protocol-Mon Feb 13, 2pm ET
Date: Monday, February 13, 2006 2:03:31 PM

Reminder for Today's call.

The best available time for the SUPPORT subcommittee to review the Ancillary protocol from Dr. Gauthier is:

Monday, February 13th,
2:00-3:00pm ET (11:00-12:00 PT)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

If you are unable to join, please circulate a written review to the group by Friday, February 10th

Thank you!
Carolyn

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Wade"; fmartinez@ucsd.edu
Subject: RE:
Date: Monday, February 13, 2006 11:41:01 AM

Hi Rose
Thanks for our phone call of this morning. I am obviously disappointed with the outcome, and would like to make every effort to try to allow us to continue to enroll. With regards to in-service for SUPPORT we can do this at the Steering Committee on the Tuesday. Do you anticipate the need for site visits to the new sites? This was an important aspect of SUPPORT in-service and could also be done by some of the other SUPPORT committee members. I am willing to do some/all of these.
One other thought would be that the coordinators could visit San Diego and have the in-service here. We will try to accommodate the Network.
I would also hope that Wade should continue to be involved in some way as he has been a fabulous resource for the coordinators and RTI. Can we try to cover his travel and some time? Wade spends almost 1-2 hours a day on SUPPORT.
I will obtain airline flights for the next Steering Committee meeting and would plan on leaving Wednesday in the morning if possible. I will think about the need to attend every Steering Committee meeting – Some may be done by Conferencing in by telephone.
Any help that you and Grace can provide would be appreciated with regards to a zero cost extension of current funds.
Regards
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, February 13, 2006 7:42 AM
To: Neil Finer
Subject: RE:

http://www.grants.nih.gov/grants/guide/notice-files/not97-232.html

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Thanks
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We were careful to state in the grant that we had designed, led and completed DR-CPAP and then followed with SUPPORT. We included our detailed design about the oximeter algorithm which is being used by virtually every other trial in the Australia, England and Canada and in the US if Cindy Cole is funded.

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Was there a program officer present during the review who could share with use any additional information?
We remain puzzled, concerned and committed.
In addition can you advise how we would best proceed to appeal this decision.
I hope that you can shed some light on this issue for us.
Many thanks
Neil

From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT DSMC POWERPOINT
Date: Saturday, February 11, 2006 4:59:19 PM

Hey- i'm so far behind that i'm afraid they will delete or archive all my unread emails if i don't . thanks .
ron

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

02/11/2006 03:42 PM

To <goldb008@mc.duke.edu>
cc
Subject Re: SUPPORT DSMC POWERPOINT

I thought you didn't check email on the weekend!!
On a positive note, I met with the grants management folks late this week and your Duke application is on the list to be funded for the NRN. As always nothing is ever final until a Notice of Grant Award gets issued, but if all goes well, this should happen within the next two weeks.

Enjoy the rest of the weekend!!

Take care
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Ronald N Goldberg <goldb008@mc.duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Sat Feb 11 16:37:39 2006
Subject: Re: SUPPORT DSMC POWERPOINT

Rose ,
i'm ok with it.
Any final word- this is killing me.
ron

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

02/10/2006 11:12 AM

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>, "Krisa VanMeurs \(VanMeurs, Krisa\)" <vanmeurs@leland.stanford.edu>, "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>, &! quot;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 "Petrie, Carolyn" <petrie@rti.org>

Subject SUPPORT DSMC POWERPOINT

Dr. William Tarnow-Mordi who is the PI for the BOOST II trial has requested information regarding the SUPPORT trial.
Dr. Barbara Schmidt has just received funding for the Canadian Oximetry trial by CIHR.

The steering committee has previously agreed to share this information in a confidential manner with Drs. Cole and Hey. Please let me know if you DISAGREE with sharing the information confidentially with DR. Tarnow-Mordi by Monday Feb. 13.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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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]
Subject: Re: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 3:30:10 PM

I agree.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: 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>; Krisa VanMeurs (VanMeurs, Krisa) <vanmeurs@leland.stanford.edu>; 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 <walid.salhab@utsouthwestern.edu>
CC: Petrie, Carolyn <petrie@rti.org>
Sent: Fri Feb 10 11:12:38 2006
Subject: SUPPORT DSMC POWERPOINT

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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:	Das, Abhik
To:	Michele Walsh; walid.salhab@utsouthwestern.edu; Tyson Jon (E-mail); [SCRN] Stoll, Barbara; Stevenson David (E-mail); Shankaran Seetha (E-mail); Shahnaz Duara; Ronald GOldberg; Poole, W. Kenneth; Oh William (E-mail); Neil Finer; Michelle Walsh; Michael O"Shea; Lemons Jim (E-mail); Krisa VanMeurs (VanMeurs, Krisa); Jobe Alan (E-mail); Ehrenkranz Richard (E-mail); Ed Donovan; Dale Phelps; Charles Rosenfeld; Carlo Waldemar (E-mail); Brenda Poindexter; alaptook@WIHRI.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Fanaroff, Avroy; Petrie, Carolyn; Poole, W. Kenneth
Subject:	RE: LB Abstract Form -version 2
Date:	Friday, February 10, 2006 2:09:45 PM

Michele:

RTI did not do the power analysis for this abstract. We only ran the logistic regression models to look at time trends of indocin use in the GDB. Indeed, Ken and I have repeatedly communicated our deep unease with this critique of the TIPP trial.

Thanks

Abhik

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Friday, February 10, 2006 1:07 PM
To: walid.salhab@utsouthwestern.edu; Tyson Jon (E-mail); [SCRN] Stoll, Barbara; Stevenson David (E-mail); Shankaran Seetha (E-mail); Shahnaz Duara; Ronald GOldberg; Poole, W. Kenneth; Oh William (E-mail); Neil Finer; Michelle Walsh; Michael O'Shea; Lemons Jim (E-mail); Krisa VanMeurs (VanMeurs, Krisa); Jobe Alan (E-mail); Ehrenkranz Richard (E-mail); Ed Donovan; Dale Phelps; Charles Rosenfeld; Carlo Waldemar (E-mail); Brenda Poindexter; Das, Abhik; alaptook@WIHRI.org; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Fanaroff, Avroy; Petrie, Carolyn
Subject: Re: LB Abstract Form -version 2

I feel the abstract is an improvement but still needs work.
Specific concerns:
1. Should specify TIPP primary outcome and not assume the reader will know what this is.
2. More importantly: In the results: "The TIPP trial hypothesized a 20% difference in primary outcome between treatment groups. Analysis of its assumptions showed that a much smaller, clinically insignificant difference
(<3%) should have been anticipated. "
[How were the assumptions analyzed? Should be included in methods. Who
did these analyses-RTI? How was clinically insignificant defined?] I do not support its submission as a late breaker in this form. Michele
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <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>; "Krisa VanMeurs (VanMeurs, Krisa)" <vanmeurs@leland.stanford.edu>; "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: "Petrie, Carolyn" <petrie@rti.org>
Sent: Friday, February 10, 2006 11:14 AM
Subject: LB Abstract Form -version 2

Hi,
Dr. Clyman has revised his abstract. The revised version is attached.
Please send me input as to submit/don't submit by Tuesday Feb. 14.

Thanks
Rose
<<LB Abstract Form -version 2.doc>>

From: Shankaran, Seetha
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 2:03:06 PM

Rose
If the request is for the same information, okay with me
Seetha

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 10, 2006 12:13 PM
To: 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); Krisa VanMeurs (VanMeurs, Krisa); 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
Subject: SUPPORT DSMC POWERPOINT

Dr. William Tarnow-Mordi who is the PI for the BOOST II trial has requested information regarding the SUPPORT trial.
Dr. Barbara Schmidt has just received funding for the Canadian Oximetry trial by CIHR.

The steering committee has previously agreed to share this information in a confidential manner with Drs. Cole and Hey. Please let me know if you DISAGREE with sharing the information confidentially with DR. Tarnow-Mordi by Monday Feb. 13.
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: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 1:51:39 PM

Rose,
I think it is fine to share the information.
Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 10, 2006 12:13 PM
To: alaptook@WIHRI.org; Abhik Das; Poindexter, Brenda B; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Krisa VanMeurs (VanMeurs, Krisa); Lemons, James A; 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
Subject: SUPPORT DSMC POWERPOINT

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

From:	Nancy Newman
To:	wrich@ucsd.edu
Cc:	ahensman@wihri.org; "Hastings, Betty J."; "Zaterka-Baxter, Kristin"; "Michele Walsh"; Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org
Subject:	RE:
Date:	Friday, February 10, 2006 1:37:47 PM

Hi Wade, I have not yet revised the OWL but intend to do so and we shoul each get some ideas and try to connect on them. The Appendix D should be the version that will be for the NRN. As well, I have not heard the decision on the time frame for the FiO2 collection for 1st 14d and the remainder of time in O2- so when that is decided we can work on the format that would best work. I think Betty may have begun to re-do the forms- we'll have to find out.....NN

From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Friday, February 10, 2006 1:18 PM
To: 'Nancy Newman'
Subject: RE:

Nancy,

I agree with you on both accounts and want to offer my services if they are desired to move this forward. We put a heck of a lot of work into this study, and I want to see it succeed. Two issues are in the forefront from my perspective:

1) Hourly data collection is not practicable when centers only gather FiO2 data every 2 or 4 hours. That is why I had Kris send out the question to the sites.
2) I agree that OWL is only a guideline, and needs some help. Have you already done something to it? If not, I am going to work on putting together a presentation which covers the high points and molds it to our needs.

wade

From: Nancy Newman [mailto:nxs5@case.edu]
Sent: Friday, February 10, 2006 9:50 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: adas@rti.org; 'Michele Walsh'; 'Hastings, Betty J.'; 'Zaterka-Baxter, Kristin'; ahensman@wihri.org; wrich@ucsd.edu; nfiner@ucsd.edu
Subject:

Hi Rose- I glad we are somewhat close to re-starting SUPPORT but I hope there will be some discussion of what new data will be collected and that a few of the coordinators can share ideas as to the best way to structure the forms. We can go back to our IRBs with the DSMC memo and minutes, but we will need the updated forms to submit and available for the new data collection before anybody should start. I would like to work on the forms and I'm not sure who is doing the re-structuring. As well, the OWL protocol needs to be customized for the NRN, as there are some points that seem to be different than what our protocol and Neil's 8-point summary detailed. I hope we can revise the necessary data collection and manual to ensure the study's success.....Nancy

From: David Stevenson
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 1:21:41 PM

Rose,

I agree.
David

At 09:12 AM 2/10/2006, you wrote:

> Dr. William Tarnow-Mordi who is the PI for the BOOST II trial has requested information regarding the SUPPORT trial.
> Dr. Barbara Schmidt has just received funding for the Canadian Oximetry trial by CIHR.
>
> The steering committee has previously agreed to share this information in a confidential manner with Drs. Cole and Hey. Please let me know if you DISAGREE with sharing the information confidentially with DR. Tarnow-Mordi by Monday Feb. 13.
> Thanks
> Rose

Rosemary D. Higgins, M.D.
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 12:27:46 PM

I agree with sharing this with Barbara and William
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 10, 2006 9:13 AM
To: 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); Krisa VanMeurs (VanMeurs, Krisa); 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
Subject: SUPPORT DSMC POWERPOINT

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Thanks
Rose

Rosemary D. Higgins, M.D.
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT DSMC POWERPOINT
Date: Friday, February 10, 2006 12:24:14 PM

ok by me.

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

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/10/2006 12:12:38 PM >>>
Dr. William Tarnow-Mordi who is the PI for the BOOST II trial has requested information regarding the SUPPORT trial.
Dr. Barbara Schmidt has just received funding for the Canadian Oximetry trial by CIHR.

The steering committee has previously agreed to share this information in a confidential manner with Drs. Cole and Hey. Please let me know if you DISAGREE with sharing the information confidentially with DR. Tarnow-Mordi by Monday Feb. 13.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From:	Charles Rosenfeld
To:	william_oh@brown.edu; edward.donovan@cchmc.org; Jobea0@chmcc.org; bpoindex@iupui.edu; jlemons@iupui.edu; vanmeurs@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]; goldb008@mc.duke.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; s_shankaran@wayne.edu; moshea@wfubmc.edu; alaptook@WIHRI.org; richard.ehrenkranz@yale.edu
Cc:	petrie@rti.org
Subject:	Re: SUPPORT DSMC POWERPOINT
Date:	Friday, February 10, 2006 12:18:33 PM

As long as the rules are the same, I guess it is okay,

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

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/10/06 11:12 AM >>>
Dr. William Tarnow-Mordi who is the PI for the BOOST II trial has requested information regarding the SUPPORT trial.

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Thanks

Rose

Rosemary D. Higgins, M.D.

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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 DSMC POWERPOINT
Date: Friday, February 10, 2006 12:17:18 PM

fine to share, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 10, 2006 12:13 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); Krisa VanMeurs (VanMeurs, Krisa); 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
Subject: SUPPORT DSMC POWERPOINT

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Thanks
Rose

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

From: Das, Abhik
To: Angelita Hensman
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Trial-Technical memo # 5
Date: Friday, February 10, 2006 11:35:41 AM

The investigators are working on the changes as we speak, and we will incorporate them in the DMS and manual asap, but we wanted to get a headstart on the process (IRBs may take some time).

Thanks

Abhik

From: Angelita Hensman [mailto:AHensman@WIHRI.org]
Sent: Friday, February 10, 2006 11:00 AM
To: Das, Abhik
Subject: RE: SUPPORT Trial-Technical memo # 5

Hi Abhik,
I understand the need to move forward quickly with restarting this trial but I am not sure I understand why the data center is giving sites the go ahead to restart the trial **before** the data forms are updated to include the data mentioned in Technical memo # 5.
Are we then going to put in **** for missing information in these fields once the new forms come out if it is not available in the record (eg, alarm limit documentation)? Since the 8 points presented to the DSMC were inherent in making the recommendation to continue the trial don't you think we should be getting the appropriate documentation at ALL sites when we restart regardless of why the trial was stopped in the first place?
Thanks
Angelita

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, February 09, 2006 1:47 PM
To: Angelita Hensman; 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; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; wrich@ucsd.edu; brenda.H.Morris@Uth.tmc.edu; cotte010@mc.duke.edu; crosen@mednet.swmed.edu; vanmeurs@leland.stanford.edu; kurt.schibler@cchmc.org; edward.donovan@chmcc.org; Abbot Laptook; bpoindex@iupui.edu; 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; Maynard.Rasmussen@sharp.com; mcw3@cwru.edu; Nirupama_Laroia@URMC.Rochester.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@UTSouthwestern.edu; [SCRN] Stoll, Barbara; dale_phelps@urmc.rochester.edu; dstevenson@stanford.edu; jon.e.tyson@uth.tmc.edu; richard.ehrenkranz@yale.edu; goldb008@mc.duke.edu; William Oh; Barbara.Alexander@cchmc.org; Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc: higginsr@mail.nih.gov; Das, Abhik; Petrie, Carolyn; Newman, Jamie; Zaterka-Baxter, Kristin
Subject: SUPPORT Trial
Importance: High

Attached is a Technical Memo #5. This memo is intended to help clarify some of the questions that have been raised about restarting the enrollment in the SUPPORT Trial. Namely, the official start date and changes to forms and MOP. The current protocol (dated 3/28/05) has not changed, however there will be some modifications to the MOP and possibly the SUPP05 form. These will be sent out to the sites just as

soon as possible.

Thanks.
Betty

<<SUP05.doc>>

Betty Hastings

RTI International
Statistics and Epidemiology
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From:	Petrie, Carolyn
To:	Petrie, Carolyn; Poole, W. Kenneth; Das, Abhik; 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:	diane.timmer@cchmc.org; fmartinez@ucsd.edu; cdg2749@yahoo.com; aellison@med.miami.edu; msumner@peds.uab.edu; Gantz, Marie; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject:	RE: SUPPORT--Ancillary: Protocol-Mon Feb 13, 2pm ET
Date:	Friday, February 10, 2006 11:05:56 AM

Reminder for Monday's call.
If you are unable to join this call, please provide your written comments by today.

Thank you!

From: Petrie, Carolyn
Sent: Monday, February 06, 2006 4:41 PM
To: Petrie, Carolyn; Poole, W. Kenneth; Das, Abhik; 'edward.donovan@chmcc.org'; 'higginsr@mail.nih.gov'; 'Michele Walsh (mcw3@cwru.edu)'; 'nfiner@ucsd.edu'; 'reverett@med.miami.edu'; 'sduara@miami.edu'; 'Wade Rich (wrich@ucsd.edu)'; 'wcarlo@peds.uab.edu'
Cc: 'Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)'; 'Fernando Martinez (fmartinez@ucsd.edu)'; 'Carolyn Grier (CWRU) (b) (6) '; 'Amanda Ellison (Miami) (aellison@med.miami.edu)'; 'msumner@peds.uab.edu'; Gantz, Marie; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: SUPPORT--Ancillary: Protocol-Mon Feb 13, 2pm ET

The best available time for the SUPPORT subcommittee to review the Ancillary protocol from Dr. Gauthier is:

Monday, February 13th,
2:00-3:00pm ET (11:00-12:00 PT)

To join the call,

Dial Toll Free, **866-675**(b) (6)
Passcode: (b) (6)

If you are unable to join, please circulate a written review to the group by Friday, February 10th

Thank you!
Carolyn

From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: re SUPPORT
Date: Thursday, February 09, 2006 4:11:25 PM

Rose: Two issues: Nancy and are feeling akward and in limbo about the status of Neil and San Diego. It is difficult as we are trying to resubmit the protocol to the IRB but we are not getting any communication from SD. For instance, we are happy to assist with the manual and protocol and form changes if needed. A coordinator from the subcommittee centers could fill in/help Wade make these changes. Nancy is happy to help, as I'm sure Monica Collins would be- but they don't want to hurt feelings. The OWL protocol sent out as Appendix D needs to be edited- or presented with a disclaimer that this is the protocol from Oschner. We probably need to adapt it for our individual centers but should all agree to the same alarm limits of 85 and 94 as in the protocol.
(OWL says 80, 95%).
2. RE the Network recompetition: We check the web sites daily for word of the official status in the Network but nothing is appearing. Can't you say something to the network in general- even if it is vague- "x sites will be funded. Not all current sites will be returning." The rumors are rampant and hurtful to the departing centers.
Regards, Michele

From: Kathy J Auten
To: wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kris Zaterka-Baxter; Nancy Peters
Subject: Re: FW: study status ???
Date: Thursday, February 09, 2006 3:43:00 PM

Then we probably should revise the SUPPORT MOP to say "Status" (meaning 120 days/transfer/death) rather than "Study Status" since it now asks for us to cease reporting on the SUPP08 at 36 weeks (Study Status). The instructions at the top of the SUPP08 should then indicate that we are to report death on that form if it is attributable to a study-related (ie., reported on the SUPP08) adverse event.
KA

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

"Wade Rich" <wrich@ucsd.edu> wrote on 02/09/2006 01:23:28 PM:

> Your answer from Rose.
>
> w
>
> From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
> Sent: Thursday, February 09, 2006 10:01 AM
> To: wrich@ucsd.edu
> Subject: RE: study status ???
>
> We should have death and ROP (especially surgery or progression of
> disease) reported as these are outcome measures.
>
> Thanks
> Rose
>
>
> From: Wade Rich [mailto:wrich@ucsd.edu]
> Sent: Thursday, February 09, 2006 11:16 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Subject: RE: study status ???
>
> Rose,
> Would you expect SAE reports fro centers for the Support trial past
> 36 weeks? For us that is study status, and anything that occurs
> after is not part of the study, and is reported elsewhere.
> Wade
>
>
> From: Kathy J Auten [mailto:auten002@mc.duke.edu]
> Sent: Thursday, February 09, 2006 7:48 AM
> To: Wade Rich
> Cc: Nancy Peters
> Subject: study status ???
>
> Wade,
> Nancy and I would like clarification on the definition of "study
> status" for SUPPORT. We are told to complete SAE information
> (SUPP08) through Study Status, which appears to equal 36 wks GA per
> protocol. If so, then we would not report death or ROP on the SUPP08
> if it occurs after 36 weeks but before d/c. I suppose the 2ndary
> outcomes of decreased incidence of death/ROP would be captured in
> the GDB, correct?
> 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

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Zaterka-Baxter, Kristin
Subject: SUP05.doc
Date: Thursday, February 09, 2006 12:42:25 PM
Attachments: SUP05.doc

Rose and Abhik,
Please look this over and make any changes/comments. This still does help with the fact that we do not have a means for collecting the additional information on the FIO2s or that the sites need the form(s) and MOP.

<<SUP05.doc>>

RTI INTERNATIONAL | Memorandum

February 9, 2006

SUPPORT TECHNICAL MEMO # 5

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: Reactivating Enrollment into the SUPPORT Trial

The DSMC for the NICHD Neonatal Research Network SUPPORT trial met with the Principle Investigator and Data Coordinating Center staff on January 24th 2006 in Washington D.C. After reviewing the data presented to the DSMC, the consensus was to restart the SUPPORT Trial. The DSMC took Dr. Finer's 8 points of proposed changes as inherent in making its recommendation to continue the trial. The DSMC also emphasized that the current protocol should be resumed and that the DSMC was not changing the protocol. The proposed changes are as follows:

1. Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours.
2. Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.
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 84% and 96%. We will use a training model based on the OWL (Oxygen with Love Program) developed at Oschner.
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.
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.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses i.e.; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

The official start date for reactivating enrollment in the SUPPORT Trial is February 6, 2006. This is the date that the official notification, from Dr. Duane Alexander was sent to the sites. Once you have received IRB approval, please resume enrollment.

Please Note: Some of the above steps are in the process of being implemented and any form and Manual of Operations changes will be forthcoming.

cc: Rosemary Higgins

From: Wally Carlo, M.D.
To: nfiner@ucsd.edu; ALaptook@wihri.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support trial
Date: Thursday, February 09, 2006 12:13:59 PM

We use the high alarm if the infant is at risk of getting O2 (eg on cpap or cannula). We use the alarm at 99 but if the baby sats at 100 we turn it off.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: 'Abbot Laptook' <ALaptook@wihri.org>
CC: 'Higgins, Rosemary (NIH/NICHD) [E]' <higginsr@mail.nih.gov>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Thu Feb 09 11:07:09 2006
Subject: RE: Support trial

Hi Abbott

I argued to the DSMC that we should NOT use a high alarm for infants in room air. Wally indicated that they do this in his unit. As the committee did not unanimously support this, I believe that the setting of a high alarm for infants in room air off of all support would not be of value, and do not think that we need to do this. The benefit of this approach is to prevent an infant from having oxygen turned on and then not given adequate attention.

I expressed the very concerns that you have indicated in favor of not using the high alarm. I do not believe that the DSMC was requiring this for the study.

Thanks for your comments

Neil

From: Abbot Laptook [mailto:ALaptook@wihri.org]
Sent: Thursday, February 09, 2006 6:49 AM
To: Neil Finer
Cc: HigginsR@mail.nih.gov; Angelita Hensman
Subject: Support trial

Neil

I need a clarification of the minutes from the DSMC: specifically the additional concern regarding use of a high alarm limit for infants in room air (set at 98%). Aren't you concerned that this will lead to unending alarms that will desensitize the bedside staff to responding to alarms outside of the goal range. We have done that on some infants that are extremely labile and who go in and out of oxygen. I think it cuts both ways; there will be some time in oxygen where there will be sats above the goal range, and there will be time in room air with sats of 98, 99 and 100% which will drive the nurses nuts with alarms constantly going off. I am more concerned about the latter for good buy in from staff. How firm will the study be regarding this? AL

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: study status ???
Date: Thursday, February 09, 2006 11:16:34 AM

Rose,
Would you expect SAE reports fro centers for the Support trial past 36 weeks? For us that is study status, and anything that occurs after is not part of the study, and is reported elsewhere.
Wade

From: Kathy J Auten [mailto:auten002@mc.duke.edu]
Sent: Thursday, February 09, 2006 7:48 AM
To: Wade Rich
Cc: Nancy Peters
Subject: study status ???

Wade,
Nancy and I would like clarification on the definition of "study status" for SUPPORT. We are told to complete SAE information (SUPP08) through Study Status, which appears to equal 36 wks GA per protocol. If so, then we would not report death or ROP on the SUPP08 if it occurs after 36 weeks but before d/c. I suppose the 2ndary outcomes of decreased incidence of death/ROP would be captured in the GDB, correct?
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

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: support
Date: Thursday, February 09, 2006 10:39:03 AM

It seems so. Neil/Wade had drafted a start-up memo but it pretty much stated the same thing that was in the DSMC memo. It also stated that there were protocol changes, which isn't correct. I can use this and draft something that you and Abhik can review. How does that sound?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 09, 2006 10:33 AM
To: Hastings, Betty J.
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: support

Betty
The data center should send the official notification. Do they need a cover letter to go with the other information?
Thanks
Rose

From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Thursday, February 09, 2006 10:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Zaterka-Baxter, Kristin
Subject: RE: support

Rose,
Some of the sites seem to be asking for an "official" memo telling them that they can start enrollment once they have received IRB approval. However, several of the sites require form and MOP changes to also submit to their IRBs. I've been communicating with Wade about the form change but we have not reached a decision about what exactly that should be. He's trying to talk to Neil (who is away) about this.

Do you want to send "official" notification to the sites or do you want something to come from the Data Center?
Thanks so much.
Betty

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 09, 2006 9:30 AM
To: Das, Abhik; Hastings, Betty J.; Zaterka-Baxter, Kristin
Subject: RE: support

I agree- start ASAP>

Rose

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, February 09, 2006 9:21 AM
To: Hastings, Betty J.; Zaterka-Baxter, Kristin
Cc: Higgins, Rosemary (NIH/NICHD) [E]

Subject: RE: support

I think we should start immediately (as long as site IRBs give their blessings), so that we dont lose any more momentum/patients. The revisions are being worked on and will be added on as soon as available/possible.

Thanks

Abhik

-----Original Message-----
From: Zaterka-Baxter, Kristin
Sent: Wednesday, February 08, 2006 3:10 PM
To: Das, Abhik
Cc: Hastings, Betty J.
Subject: support

Hi,
Just want to make sure I'm giving the sites the right information; the memos Betty sent out regarding the re-activation from both the DSMC and NICHD are saying to the site they can essentially go ahead and start enrollment (with local IRB approval) correct? Angelita has concerns that if they receive IRB approval based on these letters, and start collecting data, then the data required are modified based on the eight points defined in the DSMC minutes, she would have been collecting the wrong data. She also thinks RTI should set a 'start date' for resumption of data collection or state that revisions to the MOP and forms are forthcoming and sites should not begin data collection until these are distributed. What would your suggestions be with respect to Angelita's concerns?
Thanks,
Kris

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Neil Finer; wrich@ucsd.edu
Subject: RE: SUPPORT suspension
Date: Wednesday, February 08, 2006 10:55:01 AM

Hi Rose
I agree and would like to provide him with the information.
I would also like to suggest that at the next Steering Committee there is consideration to having a 2-3 hour in-service for SUPPORT for the new centers. If they are pre-circulated with the protocol and manual, this in-service would go a long way to getting them ready to start enrolling at their sites(s).
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2006 7:07 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT suspension

Neil
I think that William falls into the same category as Cindy and Edmund with respect to seeing the information generated in the powerpoint for SUPPORT.
I will ask the steering committee if it is ok to share the presentation confidentially with William.
Let me know if you think differently.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: ccole@bidmc.harvard.edu <ccole@bidmc.harvard.edu>
To: williamtm@med.usyd.edu.au <williamtm@med.usyd.edu.au>
CC: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Wed Feb 08 10:02:40 2006
Subject: RE: SUPPORT suspension

Hi, William,
Great to hear from you. I am returning to kicking.
I must refer you to Neil Finer and Rosemary Higgins to address questions about SUPPORT.
I will be in touch with you soon re: BOOST II, SPR, and our ongoing efforts to move the US POST pilot forward.
I very much want to learn what has transpired since September with BOOST II.
I sincerely hope you are doing well.
Kindest regards - 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

-----Original Message-----
From: williamtm@med.usyd.edu.au [mailto:williamtm@med.usyd.edu.au]
Sent: Tuesday, February 07, 2006 10:13 PM
To: Cole,Cynthia H. (HMFP - Neonatology)
Subject: SUPPORT suspension

Dear Cindy

A happy new year to you and I hope that you remain strong and kicking.

Our TSC is meeting next week and we are in a quandary as to whether to start BOOST II as we heard that SUPPORT has been temporarily suspended.

Are you able to give me any indication of why that was and what is now planned for the SUPPORT study?

William

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT DSMC Minutes
Date: Wednesday, February 08, 2006 8:51:27 AM

Not unless there is dome agreement that you have in place with them requiring you do so
---
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: Wed Feb 08 08:27:55 2006
Subject: Fw: SUPPORT DSMC Minutes

Cathy
The company that we purchase the oximeters from is requesting the information regarding the SUPPORT trial. We don't send them the memo and dsmc minutes, do we??
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Wed Feb 08 08:22:35 2006
Subject: FW: SUPPORT DSMC Minutes

Rose,
Did you receive this? It didn't appear to go through.
Thanks.
Betty
-----Original Message-----
From: Hastings, Betty J.
Sent: Tuesday, February 07, 2006 1:38 PM
To: higginsr@mail.nih.gov
Cc: Das, Abhik
Subject: FW: SUPPORT DSMC Minutes

Rose,
What do you think about sending a copy of the minutes to Masimo?
Thanks.
Betty
-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Tuesday, February 07, 2006 1:28 PM
To: Hastings, Betty J.
Subject: RE: SUPPORT DSMC Minutes

Are these minutes/letters public? Masimo would like to know what is up with the study.

wade

Attached are the following documents:

* Letter from Dr. Duane Alexander concurring with the resumption of the SUPPORT Trial with the proposed modifications as summarized in the minutes
* Letter addressed to your local IRB
* Summary of the Minutes of January 24, 2006 DSMC meeting

Please note that the clarifications for the Manual of Operations and proposed form change will be forthcoming.

Thank you. <<Dr. Alexander.pdf>> <<DSMCMemosites[01-24-06].doc>> <<DSMC Min_SUPPORT[1-24-06].doc>>
Betty

Betty Hastings

RTI International
Statistics and Epidemiology
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: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT DSMC Minutes
Date: Wednesday, February 08, 2006 8:27:59 AM

Thanks. I thought that might be the case.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2006 8:25 AM
To: Hastings, Betty J.
Subject: Re: SUPPORT DSMC Minutes

I had gotten it, but am not sure we should send it to them. The NRN has no relationship with them. We are purchasing the oximeters. I need to check with the folks at NIH. I will let you and Wade know. Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Wed Feb 08 08:22:35 2006
Subject: FW: SUPPORT DSMC Minutes

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Betty

Betty Hastings

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Fax: (919) 485-7762
bkh@rti.org <mailto:bkh@rti.org>

From:	Hastings, Betty J.
To:	charles.rosenfeld@utsouthwestern.edu; alaptook@wihri.org; aaf2@po.cwru.edu; [SCRN] Stoll, Barbara; bpoindex@iupui.edu; dale_phelps@urmc.rochester.edu; dstevenson@stanford.edu; edward.donovan@chmcc.org; 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; ahensman@wihri.org; mbball@leland.stanford.edu; grisbyca@email.uc.edu; ellen_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; Georgia F 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; Barbara.Alexander@cchmc.org; Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Poole, W. Kenneth; Zaterka-Baxter, Kristin; Petrie, Carolyn
Subject:	SUPPORT DSMC Minutes
Date:	Monday, February 06, 2006 12:40:43 PM
Attachments:	Dr. Alexander.pdf DSMCMemosites 01-24-06 .doc DSMC Min_SUPPORT 1-24-06 .doc

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Attached are the following documents:

- Letter from Dr. Duane Alexander concurring with the resumption of the SUPPORT Trial with the proposed modifications as summarized in the minutes
- Letter addressed to your local IRB
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Please note that the clarifications for the Manual of Operations and proposed form change will be forthcoming.

Thank you. <<Dr. Alexander.pdf>> <<DSMCMemosites[01-24-06].doc>> <<DSMC Min_SUPPORT[1-24-06].doc>>
Betty

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bkh@rti.org

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Child Health
and Human Development
Bethesda, Maryland 20892

January 31, 2006

To: NICHD Neonatal Research Network SUPPORT Trial Centers

From: Dr. Duane Alexander
Director, NICHD

Following review of the Data Safety and Monitoring Committee meeting minutes from January 24, 2006, I concur that the SUPPORT Trial may be resumed at the NICHD NRN sites.

Duane Alexander

DEPARTMENT OF HEALTH & HUMAN SERVICES National Institutes of Health

National Institute of Child Health and Human Development

January 24, 2006

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: DSMC recommendation for the SUPPORT Trial re-activation

On November 22, 2005 the DSMC for the Neonatal Research Network recommended stopping enrollment in the SUPPORT trial due to safety and futility concerns. Dr. Duane Alexander, Director of NICHD, reviewed their recommendation and requested that enrollment into the trial be temporarily suspended until there can be assurance that the oxygen saturations are in the planned target range.

On January 24, 2006, the DSMC convened and was presented with additional data analysis from Dr. Neil Finer, Principal Investigator for the SUPPORT Trial, on behalf of the NICHD NRN SUPPORT Subcommittee and Steering Committee. Upon consideration of the data presented, the DSMC came to a consensus and recommended the trial resume with minor modifications as outlined in the summary below.

cc: Rose Higgins
Alan Jobe
NICHD Neonatal Research Network PIs
NICHD Neonatal Research Network Coordinators
DSMC Members

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

NEONATAL RESEARCH NETWORK

DATA SAFETY AND MONITORING COMMITTEE

MINUTES

January 24, 2006

The Data Safety and Monitoring Committee for the Neonatal Research Network met on January 24, 2006 to hear the response from the SUPPORT trial investigators regarding earlier concerns voiced by the DSMC about patient safety and futility relative to the separation of the infants in the two oximetry arms, which led to suspension of recruitment into this trial on Nov 22, 2005. The DSMC members in attendance were Drs. Avery (Chair), Boyle, Gleason, Redmond, Willinger, Hunt, Allen, Thomson and Clemons. Study Investigators Dr. Finer and Dr. Carlo and the NICHD Program Scientist Dr. Higgins were present during the open session. Drs. Das and Gantz, Ms. Hastings, Ms. Zaterka-Baxter, and Ms. Petrie-Huitema from the Data Center were also present.

Introductions and welcome

Dr. Avery opened the meeting by reviewing his perception of the role of the DSMC. The NICHD has a certain domain of responsibility which partially overlaps with the DSMC. The Principal Investigators also have a certain domain of responsibility which overlaps with the DSMC. However, the DSMC is distinct and separate from the Investigators which gives them an unbiased prospective. The DSMC does not design the protocol, however they are asked to referee on points of safety and utility of the study. They are also asked to review and make comments about new protocols to ensure that the necessary elements are being tracked and monitored with respect to safety of the research subject. Safety is the highest priority for the DSMC. While the Investigators are focused on answering research questions on behalf of the public at large, the DSMC is charged foremost with their safety and also to help ensure that the research questions are being answered. Dr. Avery stated that he sees the DSMC as agents of the Institute, Investigators and the public for the purpose of looking at safety and the likelihood of achievement of the research goal.

The DSMC members agreed with Dr. Avery's interpretation and further discussed the development of a formal charter outlining the responsibility of the DSMC for the NRN. Dr. Higgins informed the members that a brief description was available in the NRN Policy and Procedures Manual (Neonatal website) and that further discussion with the NICHD Director, Dr. Alexander, would be needed to create a specific charter. Additionally, the members as well as Dr. Das, Project Director for the DCC, were in favor of convening at a minimum one face to face meeting on an annual basis with continued teleconference meetings throughout the year, as necessary.

Presentation of the SUPPORT Trial

Dr. Finer made a power point presentation in which he addressed the concerns regarding safety and exposure for the infants in the high saturation treatment group; and concerns regarding futility or lack of separation between the high and low saturation treatment groups which were raised by the DSMC during the earlier review of the SUPPORT trial data.

In conclusion, Dr. Finer proposed the following changes to SUPPORT:

- Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours
- Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.
- Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 84% and 96%. We will use a training model based on the OWL (Oxygen with Love Program) developed at Oschner.
- Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
- Place bedside cards to indicate the desired target range
- Initiate compliance monitoring visits coordinated by RTI to visit random sites
- Reanalyze group differences after an additional 100 -150 infants have been enrolled.
- Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Dr. Finer thanked the DSMC on behalf of the NRN Investigators for allowing him the opportunity to present the SUPPORT data.

Dr. Finer was asked to summarize what is being proposed to help widen the difference between the two groups. Dr. Finer restated the 8 bullets of proposed changes he made during his presentation.

Presentation of SUPPORT Interim Monitoring Data

Drs. Das and Gantz presented a report on SUPPORT patients who had experienced adverse events, including death. This report was based on the adverse event status for 231 infants who were enrolled in the SUPPORT Trial as of January 16, 2006, representing 18% of the projected study enrollment of 1310 infants.

The tracking and monitoring of adverse events included air leak, need for chest compressions and/or epinephrine in the delivery room, severe IVH (grades II-IV), pulmonary hemorrhage, nasal breakdown requiring discontinuation of nasal prongs and death.

The Committee discussed the tables that were presented and the consensus was that there were no real safety concerns regarding adverse events that had been presented so far. Dr. Avery stated that since, according to the protocol, there are 4 planned looks at the data, they would not expect to hear about any serious problems until the next planned look unless the data showed something unexpected to trigger an earlier look.

Dr. Das stated that RTI is looking at adverse events after every 60th baby is enrolled in the trial. The next review of the data will be when 25% of the infants enrolled reached status. Safety as well as efficacy data will be reviewed. The committee suggested that the ROP data would be important to evaluate at the next look because of its implications both for safety and efficacy.

Final Discussions and Recommendations

Dr. Avery asked the Committee for comments regarding the proposed changes to the study. Although there were still some concerns about compliance, the consensus was that most of the concerns about safety and futility had been alleviated. Dr. Avery agreed and stated that this is a very ambitious study and an important study to conduct. Dr. Thomson indicated that she still had issues with safety and recommended that a high alarm for infants on room air be set at 98%. The consensus was that the study should go forward.

Communication of Actions Recommendations

To summarize, Dr. Avery stated that the safety concerns were significantly alleviated and based on the new look at the data, some separation is now being seen, which is reassuring. Therefore the DSMC voted to endorse the continuation of the trial. The DSMC took Dr. Finer's 8 points of proposed changes as inherent in making its recommendation. The official statements are listed below:

Safety Concerns

Safety concerns were significantly alleviated by the new analyses presented by Dr. Finer and the SUPPORT Committee. However, the DSMC expressed some concern about small unstable babies who are attached to oxygen apparatuses, without alarms, even when in room air.

Futility Concerns

The DSMC recognizes that this is a difficult study but one of great clinical importance. Therefore in light of the new analyses presented by Dr. Finer, which reported saturation data for babies only on oxygen, they feel that there it is still the possibility of achieving some separation results.

Dr. Finer thanked the Committee for their time and diligence in reviewing the data and for making these recommendations. The investigators will do their best to get the study underway and will continue to look to the Committee for guidance.

Dr. Higgins stated that an official document will be generated by RTI that will then be presented to Dr. Alexander. Dr. Higgins asked about the 8 proposed suggestions that were presented by Dr. Finer and whether they would receive guidelines regarding these. Dr. Avery stated that these will be documented in the official minutes. However, the current protocol should be resumed and it should be emphasized that the DSMC is not changing the protocol. The 8 points are very important; however there was one additional concern. This involved turning off the upper alarms for infants on room air and the possibility of have having a high alarm set at 98% in case the infant gets some oxygen. Dr. Finer stated that in this trial "no support" includes no cannula, cpap or oxygen.

The DSMC meeting was adjourned at 1:30pm.

From: Nancy Newman
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Barbara Stoll"; "Michele Walsh"; "Ellen Hale"
Date: Monday, February 06, 2006 12:05:18 PM

Hi Rose,

After a recent suggestion to change the time point for GDB infants >=32 wks corrected age to day of life 28 for determining the need for the oxygen challenge, I began to work on the changes that would be needed on the Physiologic Def. protocol, manual, forms and the NG07 form and manual of the GDB.

The changes are enormous as each point where there is a mention of 36 wk it will need revision to clarify for infant <32 and >=32 wks and the difference in the time points for evaluation.

When I made a quick review of our patients in the last 5 yrs and the number of infants >=32 weeks I was surprised the we had more than I thought (~110, about 40 >34wks), BUT the question is how many of these infants are requiring support &/or oxygen, as many of these infants are historically SGA and often do not have many respiratory issues and are not the infants who comprise the group who we see with the diagnosis of BPD/CLD.

The time points for 32 & 33 wk infants are close- in 4 wks a 32 wk infant would be 36 wk and 28 days, and when you increase the GA it does shorten the window in weeks if you look at corrected age but will it really change our number of infants with BPD/noBPD?

How should we proceed.....Nancy

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Apr 4_5 SC Agenda 2_2_06.doc
Date: Thursday, February 02, 2006 2:23:33 PM
Attachments: Apr 4_5 SC Agenda 2_2_06.doc

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here is a very tentative agenda. I put strikethrough marks to show how the subcommittee with be without certain folks. will update the subcommittee list.

my feeling for the next SC meeting is to just have one room and each subcommitte meets, with everyone in the room. this way the new centers can observe the discussions, contribute when it is an open forum, and later decide which group they would like to join.

NICHD Neonatal Research Network Steering Committee
April 4, 2006 Bolger Center, Potomac, MD

7:00-8:30am (1.5hr) → Rm 17A	**SUPPORT /Breathing Outcomes / MRI** (Finer, ~~Duara~~, Schibler ~~Donovan~~, Carlo, Walsh, Higgins, Das, Hastings, Baxter, Petrie, Rich, Coordinators)
8:30-9:00am→ Rm. 17 A	**Publications** (Schibler ~~Donovan~~, Carlo, Goldberg, Stevenson, Shankaran, Higgins, Das)
8:30-9:00am → Rm 17 B	**Cytokines** (Carlo, Shankaran, Goldberg, ~~Phelps~~, Ehrenkranz, Tyson, Stoll, Higgins, Das)
9:00-9:30am→ Rm 17 A	**Phototherapy** (Morris, Oh, Stevenson, Tyson, ~~O'Shea~~, ~~Phelps~~, Higgins, Das, McDavid, Grisby)
9:00-9:30am→ Rm 17 B	**Genomics** (~~Duara~~, Poindexter ~~Lemons~~, Stoll, Ehrenkranz, Schibler ~~Donovan~~, Stevenson, Higgins, Das, Cotten)
9:30-11:00am(1.5hr)→ Rm 17 A	**Inositol** (Phelps, Ehrenkranz, Goldberg, Poindexter ~~Lemons~~, Laptook ~~Oh~~, ~~O'Shea~~, Higgins, Das, Hastings, Baxter, Petrie, Ball, Coordinators)
11:00-:30am (0.5hr)→ Rm 17 B	**PCV7** (D'Angio, ~~Phelps~~, Stoll, Stevenson, Carlo, ~~O'Shea~~, ~~Duara~~, Shankaran, Das, Higgins, Hastings, Baxter, Petrie)
11:30-12:30pm (1hr) → Rm 17 B	**IPGE1** (Shankaran, Poindexter ~~Lemons~~, Carlo, Finer, ~~Duara~~, Walsh, Higgins, Das, Hastings, Baxter, Petrie, Coordinators)
12:30-1:00pm	**LUNCH**
1:00-2:00pm (1hr) → Rm 17 A	**Candida** (Benjamin, Stoll, Walsh, Goldberg, ~~Phelps~~, Shankaran, ~~Duara~~, Das, Higgins, Hastings, Baxter, Petrie, Auten, N. Miller, Coordinators)
1:00-2:00pm (1hr) → Rm 17 B	**Preemie iNO** (Van Meurs, Stevenson, Poindexter ~~Lemons~~, Ehrenkranz, Higgins, Das)
2:00-2:45pm (45min)-→ Rm 17 B	**Hypothermia/aEEG / Follow Up** (Shankaran, Laptook, Ehrenkranz, Walsh, Tyson, Laptook,Schibler ~~Donovan~~, Goldberg, ~~O'Shea~~, Higgins, Das, Hastings, Baxter, Petrie, Coordinators)
2:45-3:00pm→ Rm 17 B	**Urinary Lactate Secondary to Hypothermia**
3:00-3:15pm	**Break**
3:15-4:15pm→ Rm 17 A	**Probiotics** (Oh, Ambal/Carlo, Poindexter, Stoll, Laptook, ~~Duara~~, Sanchez ~~Salhab/Rosenfeld~~, Cotten/Goldberg, Higgins, Das, Hensman, Collins)
4:15-4:45pm (0.5hr) → Rm 17 B	**EOS** (Stoll,Sanchez ~~Rosenfeld~~, ~~Duara~~, Poindexter ~~Lemons~~, Stevenson, Ehrenkranz, Goldberg, Higgins, Das, Hastings, Baxter, Petrie, Coordinators)
4:45-5:45pm (1hr)→ Rm 17 B	**GDB Subcommittee** (Stoll, Walsh, ~~Duara~~, Goldberg, ~~Oh~~, Laptook, Higgins, Das, Hastings, Baxter, Petrie, Newman, Hale, Coordinators)

NICHD Neonatal Research Network Steering Committee
April 5, 2006 Bolger Center, Potomac, MD
Room 17 North Building

7:25 AM	Welcome	Dr.Higgins
7:30 AM	NRN Overview	
7:45 AM		
8:00 AM	SUPPORT	Dr. Finer
8:15 AM	Candida	Dr. Benjamin
8:30 AM	GDB	Dr. Stoll
8:45 AM	EOS Surveillance	Dr. Stoll
9:00 AM	Cytokines	Dr. Carlo
9:15 AM	Inositol	Dr. Phelps
9:30 AM		
9:45 AM	PCV7	Dr. Phelps
10:00 AM	Benchmarking	Dr. Walsh
10:15 AM	Preemie iNO	Dr. Van Meurs
10:30 AM	Genomics	Dr. Higgins
10:45 AM	Phototherapy	Dr. Morris
11:00 AM	Protocol Review	Dr. Ehrenkranz
11:15 AM	Probiotics	Dr. Oh
11:30 AM	SOS	Dr. Oh
11:45 AM		
12:00 PM	NEC	Dr. Tyson
12:15 PM	MFMU	Dr.
12:30 PM	Hypothermia FU/aEEG	Dr. Shankaran
12:45 PM	IPGE1	Dr. Sood
1:00 PM	Lunch	
1:15 PM		
1:30 PM		
1:45 PM		
2:00 PM	Follow-up Study	Dr. Higgins
2:15 PM	Publications	Dr. Donovan
2:30 PM	RTI Report	Dr. Das
2:45 PM	New business	Dr. Higgins
3:00 PM	Adjourn	

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Friday, February 03, 2006 6:33:06 PM

I think that is the best way forward
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 03, 2006 7:37 AM
To: Neil Finer; wrich@ucsd.edu
Cc: Hastings, Betty J.; Gantz, Marie
Subject: RE: SUPPORT

So we would record oxygen 6 times per day for babies on oxygen and RA for the other children. I will get Betty to change this and send the rest of the documents to the sites.

Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, February 03, 2006 10:18 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Cc: 'Hastings, Betty J.'; 'Gantz, Marie'
Subject: RE: SUPPORT

Hi Rose
I think that for the first 14 days we should collect FiO2 hourly as this routine practice for all units. If on room air, this is still easy.
I am asking Marie for data for Oxygen use after 14 days. My initial thought is that we should collect at a minimum of every 4 hours for any infant on oxygen. Those in room air for the day would be easily noted.
In view of our increased concerns about room air and our desire to track oxygen use, this would be adequate.
If Marie's data shows anything unsuspected we can change.
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 03, 2006 5:34 AM
To: Neil Finer; wrich@ucsd.edu
Cc: Hastings, Betty J.
Subject: SUPPORT

Hi
Betty has all of the documents just about ready to go to send to the sites to resume the SUPPORT Trial. One issue needs to be addressed – we had said we were going to increased the documentation of inspired oxygen concentration – we are currently documenting three times per day – please decide how much this should be increased (e.g. 4, 5, 6 or whatever you feel is appropriate??).
Once we have that, things will be good to go.

Thanks for all the effort!
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]
Subject: RE: SUPPORT
Date: Thursday, February 02, 2006 2:42:13 PM

Agreed
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2006 11:18 AM
To: nfiner@ucsd.edu
Subject: Re: SUPPORT

Ok
He should be afforded similar treatment as the other folks doing trials.
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: Neil Finer <nfiner@pedsmail.ucsd.edu>
Sent: Thu Feb 02 14:16:14 2006
Subject: RE: SUPPORT

Hi Rose,
We don't know, but I don't think he is. We'll find out.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2006 7:23 AM
To: Neil Finer
Subject: RE: SUPPORT

Neil
Is Colin participating in any of the oximetry trials separate from the
COIN Trial?
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, February 02, 2006 10:09 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Thanks Rose
Colin Morley, PI for COIN has asked for more information, but that study
does not involve the use of the oximeters etc. I will just indicate to
him

that the issues were related to the oximeters arm, and I do not believe that
he needs to receive this. The other PI that I have not head from is Tarnow
Mordi in Australia.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2006 6:30 AM
To: Neil Finer
Subject: RE: SUPPORT

OK, thanks.

I will send it out with a note that it is to remain confidential.

Also, I have 13 yeses to sharing the slide show with Hey and Cole - I will send it to them and cc you.

Thanks again for all your help

Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, February 02, 2006 9:25 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT

Hello Rose
I absolutely agree that this should be provided to individuals at the sites.
In addition, some of the IRBs may want this information.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2006 3:30 AM
To: nfiner@ucsd.edu
Subject: SUPPORT

Neil
I was asked by one of the pi's for permission to share the support dsmc powerpoint with collegues within their institution. I think this is ok as
long as folk keep it confidential. It is important for re-invigorating the
recruitment.I would like your opinion.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Charles Rosenfeld
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 6:23:48 PM

yes

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

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/01/06 12:15 PM >>>
Hi,

The SUPPORT Trial presentation to the DSMC is attached. There are two other trials utilizing oximetry levels (Drs. Cynthia Cole and Edmund Hey) for which this is pertinent. The DSMC recommended that we communicate with these investigators and Dr. Alexander has approved a confidential release of this presentation for use with IRBs and DSMCs for related trials. Since these are data which belong to the network, your input is needed on this issue. Please send me a Yes/NO vote for sharing this presentation confidentially with the two investigators and their respective IRBs/DSMCs by Feb. 3.

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: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 4:18:16 PM

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 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 02/01/2006 1:15:34 PM >>>
Hi,
The SUPPORT Trial presentation to the DSMC is attached. There are two other trials utilizing oximetry levels (Drs. Cynthia Cole and Edmund Hey) for which this is pertinent. The DSMC recommended that we communicate with these investigators and Dr. Alexander has approved a confidential release of this presentation for use with IRBs and DSMCs for related trials. Since these are data which belong to the network, your input is needed on this issue. Please send me a Yes/NO vote for sharing this presentation **confidentially** with the two investigators and their respective IRBs/DSMCs by Feb. 3.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
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301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From:	Petrie, Carolyn
To:	Poole, W. Kenneth; Das, Abhik; 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:	diane.timmer@cchmc.org; fmartinez@ucsd.edu; cdg2749@yahoo.com; aellison@med.miami.edu; msumner@peds.uab.edu; Gantz, Marie; Petrie, Carolyn
Subject:	SUPPORT--Ancillary: Protocol
Date:	Wednesday, February 01, 2006 2:58:20 PM
Attachments:	Protocol 1.09.06.doc

I have heard from a few that sometime after 2:30pm ET on Friday, February 10th is open. Please let me know if any conflicts. Thanks!!

Please send me your availability to discuss the attached ancillary to the SUPPORT Trial (attached)

Wed. Feb 1
Thur Feb 2
Fri Feb 3

Mon Feb 6
Tues Feb 7
Wed Feb 8
Thur Feb 9
Fri Feb 10

Mon Feb 13
Tues Feb 14
Wed Feb 15
Thur Feb 16
Fri Feb 17

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 10, 2006 10:17 AM
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'
Subject: FW: SUPPORT--Ancillary: Protocol

Hello Everyone
Please have a look at this new SUPPORT ancillary. I doubt that we will get
to it at our meeting, but we will try to briefly discuss and then set up a
conference call.
See you on Thursday
Safe travels.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, January 10, 2006 4:14 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT--Ancillary: Protocol

Hi neil,
Would you like us to distribute this to the subcommittee? We could set up a
call following the steering committee meeting, perhaps within a day or 2 of
the dsmc meeting? Let me know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Barbara Stoll <barbara.stoll@oz.ped.emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; petrie@rti.org <petrie@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Jan 09 23:51:31 2006
Subject: SUPPORT--Ancillary: Protocol

<<Protocol 1.09.06.doc>>

Neil and Rose

I reviewed Neil's slides and hope that the DSMC agrees that this trial will
generate important patient care data and that we will be able to put in place additional measures to ensure separation of the groups and limit further the time at very high sat levels.

Obviously dependent on the trial starting again--
Attached is revised ancillary study for SUPPORT Trial-- with budget

Regards

BJS

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

January 7, 2006

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 SUPPORT trial. Since the analyses focus on the relationship between oxidant stress markers and alveolar macrophage maturation, samples obtained from each intubated SUPPORT baby would be compared to itself across time. With the exception of sample collection, there is no intervention to the enrolled SUPPORT patient.

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

Patient Population: Tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage analysis from participating NICHD NICUs. Locally at the Emory University NICUs, tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage functional analysis and fluid analysis from the two participating SUPPORT 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. Parental consent will be obtained for this Ancillary Study at the time of SUPPORT enrollement. Because this study involves only sample collection (tracheal aspirates) an addendum to the current SUPPORT parental consent will be required, or alternatively, obtaining IRB approval from the center for verbal consent only (as at Emory University for similar studies in the past) could be obtained.

Inclusion criteria: All newborns admitted to the NICU with gestational age of 24 0/7-27 6/7 weeks eligible and enrolled in the SUPORRT Trial 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. 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 written or verbal informed consent (Emory Univ IRB has approved verbal consent for similar studies in the past, Gauthier #388.99), the TA will be obtained at the time of routine endotracheal suctioning as outlined below in Table 1:

Table 1

Begin Enrollment	Sample 1	Birth < 24 hr age
	Sample 2	Day 1 of life
	Sample 3	Day 2 of life
	Sample 4	Day 3 of life
	Sample 5	Day 7 of life
	Sample 6-8	Day 14, 21, 28 of life respectively
End Study		

SUPPORT patients randomized and maintained on CPAP will not have sample collection. Patient sample collection will end when the patient is extubated from the ventilator or at 28 days of life if still intubated. If the enrolled baby is extubated prior to 28 days of life and then reintubated, sample collection will resume at the schedule described above until the endpoint of 28 days of life.

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 provided labeled test tube containing fixative media and labeled with the study number. These samples may be collected by the bedside nurse or respiratory therapist and then saved for the research nurse. The labeled samples will need to be stored in the refrigerator, bundled and then shipped from outlying centers on dry ice to the Neonatology Laboratory of Emory University, Atlanta, GA for analysis. For samples collected locally in Atlanta, the labeled sample will be transferred to a tube containing only nutrient media and 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 2** below. Macrophage apoptosis will be measured by fluorescent cleavage of poly (ADP-ribose) polymerase (PARP), an early indicator of the apoptosis pathway (38).

Table 2 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 for SUPPORT enrollment is ~67% of eligible infants.

6. Available population/compatibility with other ongoing protocols. Locally at the Emory University NICUs, tracheal aspirate samples from intubated SUPPORT patients will be obtained for alveolar macrophage analysis and fluid analysis from two hospitals (Crawford Long Hospital and Grady Hospital are both enrolling patients in the Support trial) 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 in SUPPORT enrolled patients 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 from intubated patients in the SUPPORT trial to obtain statistical significance in the macrophage analysis as described above. This assumes that more sites than Emory will participate. Enrollment from the entire network would increase enrollment from approximately 2 intubated patients per month enrolled in SUPPORT at Emory to approximately 10-15 patients per month. If all sites participate, study will be completed in less than 1 year.

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 of intubated SUPPORT patients, when used only for clinical indications, as per individual NICU routine. Therefore, there are no other risks to the patient from this ancillary study. There are no direct benefits for the individual subjects to participate in this proposal.

I. Budget: In order to achieve statistical significance, the budget assumes a sample size of 47 patients with 8 samples/patient for a total of 376 samples and duration of 1 year.

Nursing Budget:

~ 5 hours per patient x 47 patients = 235 hours
235 @ $32/hour = $7520 + 25% fringe ($1,880) **$ 9,400**

Laboratory Budget:

Salaries: Research Technician (Levan Gabelaie) **$ 9,500**
25% effort for 1 year (including fringe) for alveolar macrophage isolation, immuno staining and confocal immunohistochemical analysis.

Supplies:

Sample Tube Preparation	**$ 500**
Primary Antibodies for cell markers and apoptosis, Fluorescent Secondary Antibodies Fluorescent Bacteria, nutrient media	**$ 7,500**
	Total: $26,900

J. References Sited

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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, February 01, 2006 2:28:42 PM

I vote Yes
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 01, 2006 10:16 AM
To: 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); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Hastings, Betty J.
Subject: SUPPORT

Hi,
The SUPPORT Trial presentation to the DSMC is attached. There are two other trials utilizing oximetry levels (Drs. Cynthia Cole and Edmund Hey) for which this is pertinent. The DSMC recommended that we communicate with these investigators and Dr. Alexander has approved a confidential release of this presentation for use with IRBs and DSMCs for related trials. Since these are data which belong to the network, your input is needed on this issue. Please send me a Yes/NO vote for sharing this presentation **confidentially** with the two investigators and their respective IRBs/DSMCs by Feb. 3.

Thanks
Rose

Rosemary D. Higgins, M.D.
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higginsr@mail.nih.gov

From: Poindexter, Brenda B
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Lemons, James A
Subject: RE: SUPPORT
Date: Wednesday, February 01, 2006 2:27:58 PM

Rose,
We are in favor of sharing the presentation.
Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 01, 2006 1:16 PM
To: alaptook@WIHRI.org; Abhik Das; Poindexter, Brenda B; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Krisa VanMeurs (VanMeurs, Krisa); Lemons, James A; 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; Zaterka-Baxter, Kristin; Hastings, Betty J.
Subject: SUPPORT

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Thanks
Rose

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From: Abbot Laptook
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: William Oh
Subject: RE: SUPPORT
Date: Wednesday, February 01, 2006 2:17:50 PM

Yes. AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 01, 2006 1:16 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); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Hastings, Betty J.
Subject: SUPPORT

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Thanks
Rose

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From: Ronald N Goldberg
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 2:14:15 PM

---

yes

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

02/01/2006 01:15 PM

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>, "Krisa VanMeurs \(VanMeurs, Krisa\)" <vanmeurs@leland.stanford.edu>, "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 "Petrie, Carolyn" <petrie@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Hastings, Betty J." <bkh@rti.org>

Subject SUPPORT

Hi,
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Thanks
Rose

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higginsr@mail.nih.gov
[attachment "DSMC Jan 18 - Handout.ppt" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]

From: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SITE VISITS
Date: Wednesday, February 01, 2006 2:09:47 PM

Jsut seems most prudent to do that as the protocol may change, etc
---
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: Wed Feb 01 14:08:59 2006
Subject: RE: SUPPORT SITE VISITS

We can do this.
Thanks
Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Wednesday, February 01, 2006 2:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SITE VISITS

Why not use people who are at active sites?

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: Wed Feb 01 14:04:28 2006
Subject: RE: SUPPORT SITE VISITS

The sites that fall out will not recruit following April 1 - these coordinators are very knowledgeable with the protocol and forms and it would be very easy for them to do this - I need your opinion on this, though.

Rose

-----Original Message-----
From: Spong, Catherine (NIH/NICHD) [E]
Sent: Wednesday, February 01, 2006 2:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT SITE VISITS

Why would you want to use them vs people from active sites?
If it is to use up money they have at their sites I can understand...

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: Wed Feb 01 14:01:04 2006
Subject: SUPPORT SITE VISITS

Hi Cathy,

We had arranged with the DSMC and RTI that site visits would be done for SUPPORT for medical monitoring. Would a possibility be to potentially have coordinators from sites that did not recompete successfully to have RTI contract with them to do the visits/
Let me know what you think.

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

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From: Richard Ehrenkranz
To: Higgins, Rosemary (NIH/NICHD) [E]; alaptook@WIHRI.org; Abhik Das; Brenda Poindexter; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Jobe Alan (E-mail); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Hastings, Betty J.
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 1:51:22 PM

Yes.
Richard

At 01:15 PM 2/1/2006, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Hi,
> The SUPPORT Trial presentation to the DSMC is attached. There are two other trials utilizing oximetry levels (Drs. Cynthia Cole and Edmund Hey) for which this is pertinent. The DSMC recommended that we communicate with these investigators and Dr. Alexander has approved a confidential release of this presentation for use with IRBs and DSMCs for related trials. Since these are data which belong to the network, your input is needed on this issue. Please send me a Yes/NO vote for sharing this presentation **confidentially** with the two investigators and their respective IRBs/DSMCs by Feb. 3.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
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Richard A. Ehrenkranz, MD
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Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

please notify the sender immediately and destroy this message. Thank you.

From: Alan Jobe
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 1:34:54 PM

Yes – perhaps my last vote!
--
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: Michael O`Shea
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT
Date: Wednesday, February 01, 2006 1:23:28 PM

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 01, 2006 1:16 PM
To: 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); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Hastings, Betty J.
Subject: SUPPORT

Hi,
The SUPPORT Trial presentation to the DSMC is attached. There are two other trials utilizing oximetry levels (Drs. Cynthia Cole and Edmund Hey) for which this is pertinent. The DSMC recommended that we communicate with these investigators and Dr. Alexander has approved a confidential release of this presentation for use with IRBs and DSMCs for related trials. Since these are data which belong to the network, your input is needed on this issue. Please send me a Yes/NO vote for sharing this presentation **confidentially** with the two investigators and their respective IRBs/DSMCs by Feb. 3.

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: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT
Date: Wednesday, February 01, 2006 11:17:58 PM

Yes-- if confidential
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: Spong, Catherine (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: DSMC Jan 18 - Handout.ppt
Date: Wednesday, February 01, 2006 8:42:11 AM

Yes I think this 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>; Hanson, James (NIH/NICHD) [E] <hansonj@mail.nih.gov>; Alexander, Duane (NIH/NICHD) [E] <alexandd@exchange.nih.gov>
Sent: Wed Feb 01 08:31:34 2006
Subject: DSMC Jan 18 - Handout.ppt

Hi,
This is the PowerPoint presentation that Dr. Finer shared with the DSMC for SUPPORT on behalf of the network. Two other pulse oximetry studies (one funded through the medical research council in England) have asked for information regarding our study temporarily halting recruitment. Can this be shared confidentially with the IRB's and DSMC's for these studies?
Thanks
Rose

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: DSMC Notes
Date: Tuesday, January 31, 2006 4:05:39 PM

I think I need to send this to the other members of the DSMC for their comments also.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 31, 2006 3:55 PM
To: Hastings, Betty J.
Subject: RE: FW: DSMC Notes

This is fine. Can you add it and then I think this will be ready to go to the sites.

Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Tuesday, January 31, 2006 3:54 PM
To: Das, Abhik
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: FW: DSMC Notes

FYI.

-----Original Message-----
From: Gordon Avery [(b) (6)
Sent: Tuesday, January 31, 2006 3:48 PM
To: Hastings, Betty J.
Subject: RE: FW: DSMC Notes

Betty, you did a good job of summarizing a very complicated discussion. My
only addition would be to the Communications of Actions and Recommendations
section. I intended to state that the DSMC took Dr. Finer's eight points as
inherent in making its recommendation.

>From: "Hastings, Betty J." <bkh@rti.org>
>To: <(b) (6)
>Subject: FW: DSMC Notes
>Date: Tue, 31 Jan 2006 10:22:34 -0500
>
>Dr. Avery,
>Just checking to make sure that you have received these. Thanks so much

>again for your time. Betty

>
> > -----Original Message-----
> > From: Hastings, Betty J.
> > Sent: Friday, January 27, 2006 1:42 PM
> > To: M. D. Gordon Avery ([redacted]
> > Subject: DSMC Notes
> >
> > Dr. Avery,
> > Attached are the minutes from the January 24th DSMC meeting. Could
> > you please review these and send me your comments. I realize they
> > are pretty long and I apologize since I know you like more concise
> > notes. Thanks so much for your time. Betty
> > <<Draft DSMC Minutes SUPPORt 1-24-06 adrev2.doc>>
> > Betty Hastings
> >
> > RTI International
> > Statistics and Epidemiology
> > P.O. Box 12194
> > Research Triangle Park, NC 27709-2194
> > Telephone: (919) 485-7740
> > Fax: (919) 485-7762
> > bkh@rti.org
> >

><< DraftDSMCMinutesSUPPORt1-24-06adrev2.doc >>

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Draft DSMC MinSUPPORT[Red 1-24-06].doc
Date: Friday, January 27, 2006 3:04:31 PM
Attachments: Draft DSMC MinSUPPORT Red 1-24-06 .doc

Rose,
I cut this down to 3 pages. I removed some of the points Neil discussed on his slides and also removed your questions to the DSMC (hope that was okay) and also IPGE. Let me know if you think this is sufficient.

Thanks.

<<Draft DSMC MinSUPPORT[Red 1-24-06].doc>>

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

NEONATAL RESEARCH NETWORK

DATA SAFETY AND MONITORING COMMITTEE

DRAFT MINUTES

January 24, 2006

The Data Safety and Monitoring Committee for the Neonatal Research Network met on January 24, 2006 to hear the response from the SUPPORT trial investigators regarding earlier concerns voiced by the DSMC about patient safety and futility relative to the separation of the infants in the two oximetry arms, which led to suspension of recruitment into this trial on Nov 22, 2005. The DSMC members in attendance were Drs. Avery (chair), Boyle, Gleason, Redmond, Willinger, Hunt, Allen, Thomson and Clemons. Study Investigators Dr. Finer and Dr. Carlo and the NICHD Program Scientist Dr. Higgins were present during the open session. Drs. Das and Gantz, Ms. Hastings, Ms. Zaterka-Baxter, and Ms. Petrie-Huitema from the Data Center were also present.

Introductions and welcome

Dr. Avery opened the meeting by reviewing his perception of the role of the DSMC. The NICHD has a certain domain of responsibility which partially overlaps with the DSMC. The Principal Investigators also have a certain domain of responsibility which overlaps with the DSMC. However, the DSMC is distinct and separate from the Investigators which gives them an unbiased prospective. The DSMC does not design the protocol, however they are asked to referee on points of safety and utility of the study. They are also asked to review and make comments about new protocols to ensure that the necessary elements are being tracked and monitored with respect to safety of the research subject. Safety is the highest priority for the DSMC. While the Investigators are focused on answering research questions on behalf of the public at large, the DSMC is charged foremost with their safety and also to help ensure that the research questions are being answered. Dr. Avery stated that he sees the DSMC as agents of the Institute, Investigators and the public for the purpose of looking at safety and the likelihood of achievement of the research goal.

The DSMC members agreed with Dr. Avery's interpretation and further discussed the development of a formal charter outlining the responsibility of the DSMC for the NRN. Dr. Higgins informed the members that a brief description was available in the NRN Policy and Procedures Manual (Neonatal website) and that further discussion with the NICHD Director, Dr. Alexander, would be needed to create a specific charter. Additionally, the members as well as Dr. Das, Project Director for the DCC, were in favor of convening at a minimum one face to face meeting on an annual basis with continued teleconference meetings throughout the year, as necessary.

Presentation of the SUPPORT Trial

Dr. Finer made a power point presentation (attached to this document) in which he addressed the concerns regarding safety and exposure for the infants in the high saturation treatment group; and concerns regarding futility or lack of separation between the high and low saturation treatment groups which were raised by the DSMC during the earlier review of the SUPPORT trial data.

In conclusion, Dr. Finer proposed the following changes to SUPPORT:

- Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours
- Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.
- Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 84% and 96%. We will use a training model based on the OWL (Oxygen with Love Program) developed at Oschner.
- Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
- Place bedside cards to indicate the desired target range
- Initiate compliance monitoring visits coordinated by RTI to visit random sites
- Reanalyze group differences after an additional 100 -150 infants have been enrolled.
- Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Dr. Finer thanked the DSMC on behalf of the NRN Investigators for allowing him the opportunity to present the SUPPORT data.

Dr. Finer was asked to summarize what is being proposed to help widen the difference between the two groups. Dr. Finer restated the 8 bullets of proposed changes he made during his presentation.

Presentation of SUPPORT Interim Monitoring Data

Drs. Das and Gantz presented a report on SUPPORT patients who had experienced adverse events, including death. This report was based on the adverse event status for 231 infants who were enrolled in the SUPPORT Trial as of January 16, 2006, representing 18% of the projected study enrollment of 1310 infants.

The tracking and monitoring of adverse events included air leak, need for chest compressions and/or epinephrine in the delivery room, severe IVH (grades II-IV), pulmonary hemorrhage, nasal breakdown requiring discontinuation of nasal prongs and death.

The Committee discussed the tables that were presented and the consensus was that there were no real safety concerns regarding adverse events that had been presented so far. Dr. Avery stated that since, according to the protocol, there are 4 planned looks at the data, they would not expect to hear about any serious problems until the next planned look unless the data showed something unexpected to trigger an earlier look.

Dr. Das stated that RTI is looking at adverse events after every 60th baby is enrolled in the trial. The next review of the data will be when 25% of the infants enrolled reached status. Safety as well as efficacy data will be reviewed. The committee suggested that the ROP data would be important to evaluate at the next look because of its implications both for safety and efficacy.

Final Discussions and Recommendations

Dr. Avery asked the Committee for comments regarding the proposed changes to the study. Although there were still some concerns about compliance, the consensus was that most of the concerns about safety and futility had been alleviated. Dr. Avery agreed and stated that this is a very ambitious study and an important study to conduct. Dr. Thomson indicated that she still had issues with safety and recommended that a high alarm for infants on room air be set at 98%. The consensus was that the study should go forward.

Communication of Actions Recommendations

To summarize, Dr. Avery stated that the safety concerns were significantly alleviated and based on the new look at the data, some separation is now being seen, which is reassuring. Therefore the DMSC voted to endorse the continuation of the trial. The official statements are listed below:

Safety Concerns

Safety concerns were significantly alleviated by the new analyses presented by Dr. Finer and the SUPPORT Committee. However, the DSMC expressed some concern about small unstable babies who are attached to oxygen apparatuses, without alarms, even when in room air.

Futility Concerns

The DSMC recognizes that this is a difficult study but one of great clinical importance. Therefore in light of the new analyses presented by Dr. Finer, which reported saturation data for babies only on oxygen, they feel that there it is still the possibility of achieving some separation results.

Dr. Finer thanked the Committee for their time and diligence in reviewing the data and for making these recommendations. The investigators will do their best to get the study underway and will continue to look to the Committee for guidance.

Dr. Higgins stated that an official document will be generated by RTI that will then be presented to Dr. Alexander. Dr. Higgins asked about the 8 proposed suggestions that were presented by Dr. Finer and whether they would receive guidelines regarding these. Dr. Avery stated that these will be documented in the official minutes. However, the current protocol should be resumed and it should be emphasized that the DSMC is not changing the protocol. The 8 points are very important; however there was one additional concern. This involved turning off the upper alarms for infants on room air and the possibility of have having a high alarm set at 98% in case the infant gets some oxygen. Dr. Finer stated that in this trial "no support" includes no cannuala, cpap or oxygen.

The DSMC meeting was adjourned at 1:30pm.

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC Minutes
Date: Friday, January 27, 2006 2:20:48 PM

Do you mean to shorten the minutes to make them more concise? I agree that they are too detailed and we can cut out a lot and just state the reasons for continuing the study.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 27, 2006 1:40 PM
To: Hastings, Betty J.
Subject: Re: DSMC Minutes

That sounds great! Are my suggestions reasonable or overkill? I would like your opinion. Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Jan 27 13:36:22 2006
Subject: RE: DSMC Minutes

Okay, once we have Dr. Avery's and the other DSMCs review, I can change these. Does that sound okay?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 27, 2006 1:34 PM
To: Hastings, Betty J.
Subject: Re: DSMC Minutes

I think these minutes are too detailed to go the the sites. They need the salient features of the support trial discussion, but not the administrative issues with the dsmc etc. Also, the ipge info should probably be separate as this is a separate study for the irbs.

Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Jan 27 13:30:15 2006
Subject: RE: DSMC Minutes

They will go to the study sites along with the memo. I did see that IPGE is on clinical hold. Wonder if it will ever go forward.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 27, 2006 1:25 PM
To: Hastings, Betty J.
Subject: Re: DSMC Minutes

Betty
These look great - do they go to the study sites or just the memo? Also, did you see that the ipge ind is on clinical hold?? Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Jan 27 13:04:13 2006
Subject: DSMC Minutes

Rose,
Here are the draft DSMC minutes. Abhik looked at these and said to send them to Dr. Avery. I told him that I would send them to you first. I sure hope these are okay. They seemed especially hard to write up.

Thanks.
Betty
<<Draft DSMC Minutes SUPPORt 1-24-06 adrev2.doc>>
Betty Hastings

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Fax: (919) 485-7762
bkh@rti.org <mailto:bkh@rti.org>

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: DSMCMemosites 01-24-06 .doc
Date: Friday, January 27, 2006 1:33:05 PM
Attachments: DSMCMemosites 01-24-06 .doc

Sorry, I corrected Dr. Alexander's name.

<<DSMCMemosites 01-24-06 .doc>>

DEPARTMENT OF HEALTH & HUMAN SERVICES National Institutes of Health

National Institute of Child Health and Human Development

January 24, 2006

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: DSMC recommendation for the SUPPORT Trial re-activation

On November 22, 2005 the DSMC for the Neonatal Research Network recommended stopping enrollment in the SUPPORT trial due to safety and futility concerns. Dr Duane Alexander, Director of NICHD, reviewed their recommendation and requested that enrollment into the trial be temporarily suspended until there can be assurance that the oxygen saturations are in the planned target range.

On January 24, 2006, the DSMC convened and was presented with additional data analysis from Dr. Neil Finer, Principal Investigator for the SUPPORT Trial, on behalf of the NICHD NRN SUPPORT Subcommittee and Steering Committee. Upon consideration of the data presented, the DSMC came to a consensus and recommended the trial resume with minor modifications as outlined in the summary below.

cc: Rose Higgins
Alan Jobe
NICHD Neonatal Research Network PIs
NICHD Neonatal Research Network Coordinators
DSMC Members

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC Minutes
Date: Friday, January 27, 2006 1:20:35 PM

Do I need to give him more details of the closed session? I think it will be fine for him to see as well. What do we do with Dr. Alexander's statement, add it like we did before when the study was stopped? Let me know if you need some additional information.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 27, 2006 1:17 PM
To: Hastings, Betty J.
Subject: Re: DSMC Minutes

This is fine except " Duane" for Dr. Alexander. I will look at the minutes and get back to you. Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Jan 27 13:14:44 2006
Subject: RE: DSMC Minutes

Rose,
I didn't put anything in there that you can't see. I didn't give any results of the Adverse events that Abhik presented. I think it should be okay for you to look at.

Here is the draft letter to the sites IRBs.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 27, 2006 1:07 PM
To: Hastings, Betty J.
Subject: Re: DSMC Minutes

Betty
Before I open the attachment, are these both from the open and closed protion of the meeting?? I am not allowed to see the closed protion minutes. Let me know and I can review them asap. Also, do you have a letter for the irb's drafted? Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Hastings, Betty J. <bkh@rti.org>

To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Fri Jan 27 13:04:13 2006
Subject: DSMC Minutes

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Thanks.
Betty
<<Draft DSMC Minutes SUPPORt 1-24-06 adrev2.doc>>
Betty Hastings

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Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org <mailto:bkh@rti.org>

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC Minutes
Date: Friday, January 27, 2006 1:14:50 PM
Attachments: DSMCMemosites[01-24-06].doc

Rose,
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Sent: Friday, January 27, 2006 1:07 PM
To: Hastings, Betty J.
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Subject: DSMC Minutes

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Betty Hastings

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DEPARTMENT OF HEALTH & HUMAN SERVICES National Institutes of Health

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January 24, 2006

MEMORANDUM

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cc: Rose Higgins
Alan Jobe
NICHD Neonatal Research Network PIs
NICHD Neonatal Research Network Coordinators
DSMC Members

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: DSMC Minutes
Date: Friday, January 27, 2006 1:04:17 PM
Attachments: Draft DSMC Minutes SUPPORt 1-24-06 adrev2.doc

Rose,
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Thanks.
Betty

<<Draft DSMC Minutes SUPPORt 1-24-06 adrev2.doc>>

Betty Hastings

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The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

NEONATAL RESEARCH NETWORK

DATA SAFETY AND MONITORING COMMITTEE

DRAFT MINUTES

January 24, 2006

The Data Safety and Monitoring Committee for the Neonatal Research Network met on January 24, 2006 to hear the response from the SUPPORT trial investigators regarding earlier concerns voiced by the DSMC about patient safety and futility relative to the separation of the infants in the two oximetry arms, which led to suspension of recruitment into this trial on Nov 22, 2005. The DSMC members in attendance were Drs. Avery (chair), Boyle, Gleason, Redmond, Willinger, Hunt, Allen, Thomson and Clemons. Study Investigators Dr. Finer and Dr. Carlo and the NICHD Program Scientist Dr. Higgins were present during the open session. Drs. Das and Gantz, Ms. Hastings, Ms. Zaterka-Baxter, and Ms. Petrie-Huitema from the Data Center were also present.

Introductions and welcome

Dr. Avery opened the meeting by reviewing his perception of the role of the DSMC. The NICHD has a certain domain of responsibility which partially overlaps with the DSMC. The Principal Investigators also have a certain domain of responsibility which overlaps with the DSMC. However, the DSMC is distinct and separate from the Investigators which gives them an unbiased prospective. The DSMC does not design the protocol, however they are asked to referee on points of safety and utility of the study. They are also asked to review and make comments about new protocols to ensure that the necessary elements are being tracked and monitored with respect to safety of the research subject. Safety is the highest priority for the DSMC. While the Investigators are focused on answering research questions on behalf of the public at large, the DSMC is charged foremost with their safety and also to help ensure that the research questions are being answered. Dr. Avery stated that he sees the DSMC as agents of the Institute, Investigators and the public for the purpose of looking at safety and the likelihood of achievement of the research goal.

The DSMC members agreed with Dr. Avery's interpretation and further discussed the development of a formal charter outlining the responsibility of the DSMC for the NRN. Dr. Higgins informed the members that a brief description was available in the NRN Policy and Procedures Manual (Neonatal website) and that further discussion with the NICHD Director, Dr. Alexander, would be needed to create a specific charter. Additionally, the members as well as Dr. Das, Project Director for the DCC, were in favor of convening at a minimum one face to face meeting on an annual basis with continued teleconference meetings throughout the year, as necessary.

Presentation of the SUPPORT Trial

Dr. Finer made a power point presentation (attached to this document) in which he addressed the concerns regarding safety and exposure for the infants in the high saturation treatment group; and concerns regarding futility or lack of separation between the high and low saturation treatment groups which were raised by the DSMC during the earlier review of the SUPPORT trial data. The following points were discussed:

Summary of Responses

- There is paucity of information regarding the usual or ideal duration of SpO2 above 95% for ELBW infants.
- Infants in room air have significantly greater durations of SpO2 values >95% than infants receiving oxygen.
- Once data analysis was corrected for the effect of room air, the durations of SpO2 >95% became markedly shorter.
- Study groups do show a modest difference for saturation exposure.
- The oximeter groups differ by 12% in their durations in room air with the 85%-89% Group spending more time in room air.
- Plans were presented to improve both separation and reduce durations of elevated SpO2

Additional points presented

- Design Parameters of the Oximeter Arm
- Evidence for Currently used SpO2 Ranges is Lacking
- Evidence for Currently used SpO2 Ranges is Lacking but Needed
- Current Best Evidence - Hagadorn et al
- Additional Evidence
- Effects of Room Air on SpO2 >95%
- Sp02 Values of Support for infants in Room Air
- Durations of SpO2 >96% fro infants in Room Air and Oxygen- Support Trial Data
- The Saturation Algorithm
- Evaluation of SpO2 Information
- Evaluation of SpO2 Ranges
- Impact of including infants in Oxygen for a portion of the day
- Initial RTI Analyses
- Corrected RTI Analyses
- Safety Issue of SpO2 >95% (Summary)
- Futility Regarding Separation of Oximeter Groups
- Cumulative SpO2 Durations Based on Oxygen Days

In conclusion, Dr. Finer proposed the following changes to SUPPORT:

- Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours
- Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.
- Further training and in-service at all the sites to stress the importance of keeping the SpO2 alarms functional and at the limits of 84% and 96%. We will use a

training model based on the OWL (Oxygen with Love Program) developed at Oschner.

- Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation
- Place bedside cards to indicate the desired target range
- Initiate compliance monitoring visits coordinated by RTI to visit random sites
- Reanalyze group differences after an additional 100 -150 infants have been enrolled.
- Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Dr. Finer thanked the DSMC on behalf of the NRN Investigators for allowing him the opportunity to present the SUPPORT data.

Dr. Finer was asked to summarize what is being proposed to help widen the difference between the two groups. Dr. Finer restated the 8 bullets of proposed changes he made during his presentation.

Dr. Higgins stated that the Institute has been approached by investigators planning similar trials, specifically by Dr. Cole, the PI of Post-ROP trial, who wanted to know more details about the status of this trial. Dr. Higgins stated that she would like the DSMC to give them guidance on what should be said publicly regarding the suspension of the SUPPORT trial.

Dr. Higgins also presented another issue for the DSMCs thoughts and consideration. Given all the analyses that have been done, with the insights regarding the effect of room air on pulse oxygen saturation levels, she asked the DSMC to consider whether it would be appropriate to use these data to write a manuscript and/or perhaps present this data at a national meeting in order to assist other investigators who are planning similar trials.

Presentation of SUPPORT Interim Monitoring Data

Drs. Das and Gantz presented a report on SUPPORT patients who had experienced adverse events, including death. This report was based on the adverse event status for 231 infants who were enrolled in the SUPPORT Trial as of January 16, 2006, representing 18% of the projected study enrollment of 1310 infants.

The tracking and monitoring of adverse events included air leak, need for chest compressions and/or epinephrine in the delivery room, severe IVH (grades II-IV), pulmonary hemorrhage, nasal breakdown requiring discontinuation of nasal prongs and death.

The Committee discussed the tables that were presented and the consensus was that there were no real safety concerns regarding adverse events that had been presented so far. Dr. Avery stated that since, according to the protocol, there are 4 planned looks at the data, they would not expect to hear about any serious problems until the next planned look unless the data showed something unexpected to trigger an earlier look. Dr. Das stated that RTI is looking at adverse events after every 60th baby is enrolled in the trial. The next review of the data will be when 25% of the infants enrolled reached status. Safety as well as efficacy data will be reviewed. The committee suggested that

the ROP data would be important to evaluate at the next look because of its implications both for safety and efficacy.

Final Discussions and Recommendations

Dr. Avery asked the Committee for comments regarding the proposed changes to the study. Although there were still some concerns about compliance, the consensus was that most of the concerns about safety and futility had been alleviated. Dr. Avery agreed and stated that this is a very ambitious study and an important study to conduct. Dr. Thomson indicated that she still had issues with safety and recommended that a high alarm for infants on room air be set at 98%. The consensus was that the study should go forward.

Open Session

Communication of Actions Recommendations

To summarize, Dr. Avery stated that the safety concerns were significantly alleviated and based on the new look at the data, some separation is now being seen, which is reassuring. Therefore the DMSC voted to endorse the continuation of the trial. The official statements are listed below:

Safety Concerns
Safety concerns were significantly alleviated by the new analyses presented by Dr. Finer and the SUPPORT Committee. However, the DSMC expressed some concern about small unstable babies who are attached to oxygen apparatuses, without alarms, even when in room air.

Futility Concerns
The DSMC recognizes that this is a difficult study but one of great clinical importance. Therefore in light of the new analyses presented by Dr. Finer, which reported saturation data for babies only on oxygen, they feel that there it is still the possibility of achieving some separation results.

The DSMC Response to Dr. Higgins

In response to Dr. Higgins' request regarding communication to other study investigators about the status of the Trial, the consensus of the DSMC is that this is not a suitable role for the DSMC. However, the DSMC encourages Dr. Higgins to communicate to these investigators that the DSMC had safety issues related to time in high oxygen and a futility issue related to how much separation was being seen between the high and low oxygen groups. The study was subsequently re-analyzed in a different way and these concerns were alleviated to the DSMC's satisfaction. The DSMC is happy for the Institute or the Steering Committee to refer to their report for this purpose.

In response to Dr. Higgins' request regarding the manuscript and/or presentation of the data at a national meeting. The DSMC recommends that to be collegial, the study can be discussed with colleagues informally to share insights into what been learned in this study but does not feel that anything should be written up or published. Since this study

is in progress, they should be mindful of the fact that there is a planned review of the data when 25% of the infants enrolled have reach status.

Dr. Finer thanked the Committee for their time and diligence in reviewing the data and for making these recommendations. The investigators will do their best to get the study underway and will continue to look to the Committee for guidance.

Dr. Higgins stated that an official document will be generated by RTI that will then be presented to Dr. Alexander. Dr. Higgins asked about the 8 proposed suggestions that were presented by Dr. Finer and whether they would receive guidelines regarding these. Dr. Avery stated that these will be documented in the official minutes. However, the current protocol should be resumed and it should be emphasized that the DSMC is not changing the protocol. The 8 points are very important; however there was one additional concern. This involved turning off the upper alarms for infants on room air and the possibility of have having a high alarm set at 98% in case the infant gets some oxygen. Dr. Finer stated that in this trial "no support" includes no cannuala, cpap or oxygen.

IPGE

On Behalf of Dr. Beena Sood, Dr Higgins presented an overview of the proposed IPGE pilot study. Dr. Higgins began this presentation with a brief description of NHRF, current treatments, their drawbacks, and the need for newer therapies. Dr. Higgins presented studies of inhaled prostaglandins in animals human adults, children and neonate. The presentation moved forward with a description of the study hypothesis, study aims, trial design, sample size, methods, patient management, exit criteria and safety monitoring. Dr. Higgins concluded the presentation, opened the floor for discussion and welcomed comments from the DSMC.

The DSMC asked about the need for therapies other than iNO. Dr. Higgins responded by stating that a small population of infants do not respond to iNO therapy. Additionally, $IPGE_1$ and iNO may have synergistic effects.

The DSMC had questions about the rate of IPGE administration and placement of the aerosol in the ventilator circuit. Dr. Higgins responded that the rate was 2ml/hr and explained that the best place to insert the aerosol in the vent circuit continues to be discussed.

The DSMC referred to page 18 of the protocol and wanted to clarification on "Some evidence of efficacy: Relative risk of 67% (range 50 – 80%) for treatment compared to control arm for progression of OI to $\geq$ 25." Dr. Das stated 'efficacy' was a secondary outcome and agreed to explore the possibility of revisiting this statement .

The DSMC questioned whether randomization stratified by center was feasible in such a small study. Dr. Das responded that stratification by center was appropriate when only six NRN centers planned to participate. However, centralized randomization without stratification by site may now be necessary.

Dr. Higgins asked if the DSMC had any safety concerns. The DSMC discussed the percent NaCl delivery and whether the amount administered per study was of concern in elevating serum sodium. Dr. Higgins stated that the NRN Indiana center looked at this issue and results were reassuring that the sodium levels were not elevated.

The DSMC meeting was adjourned with consensus on the $IPGE_1$ study pending.

From:	Neil Finer
To:	"Zaterka-Baxter, Kristin"
Cc:	nfiner@ucsd.edu; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: DSMC PPt presentation
Date:	Thursday, January 26, 2006 6:55:50 PM
Attachments:	DSMC Presentation Jan 24 I.ppt

Hi Kris
Here is the actual presentation as given to the DSMC
Regards
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 26, 2006 9:53 AM
To: Neil Finer
Cc: fmartinez@ucsd.edu; Hastings, Betty J.
Subject: DSMC PPt presentation

Hi Dr. Finer,
Would it be possible to get a copy of your power point that you presented to the DSMC so we can include this along with the re-activation letter in what we finally distribute to the sites.
Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 24, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became markedly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by 12% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- **The optimal saturation range for ELBW is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Design Parameters of Oximeter Arm

Challenges in developing the algorithm for the SUPPORT Oximeters

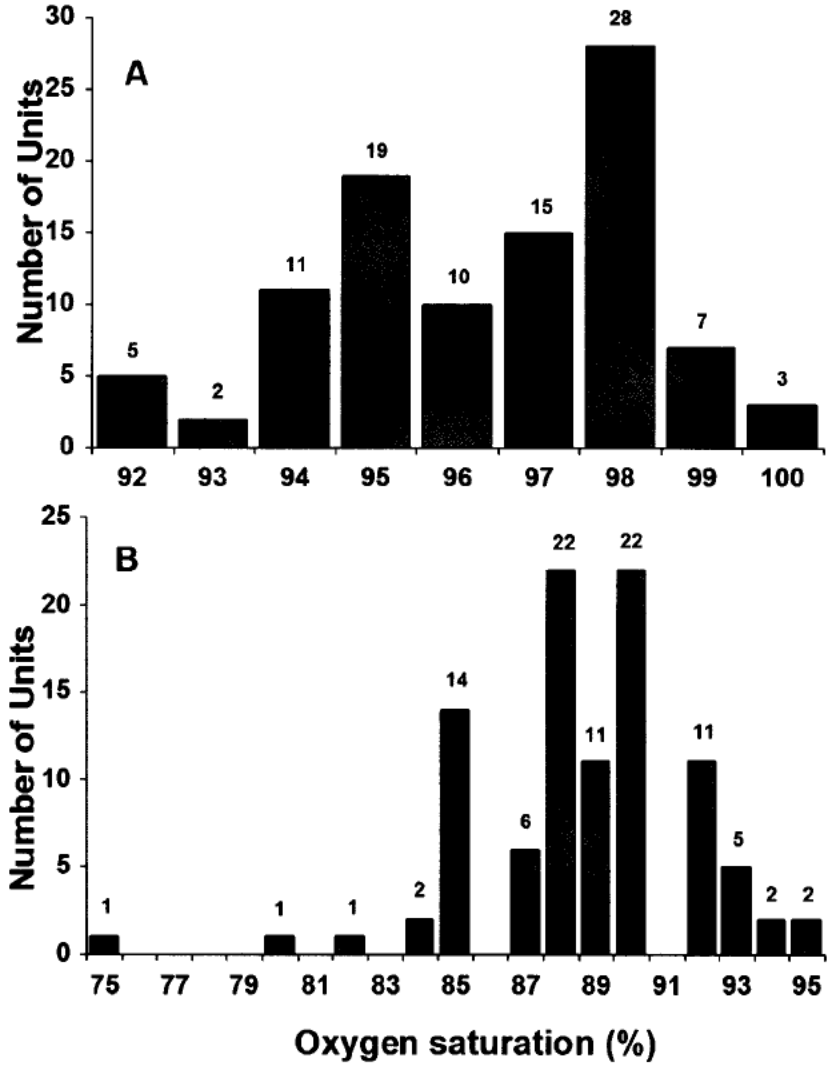
- **Maintain current Alarm limits – 85% to 95%**
- **Display real SpO2 values < 85% and > 95%**
- **Achieve a significant separation between the groups for exposures to oxygen**
- **We revised initial algorithm to achieve better separation**
- **Avoid excessive durations of both low and high SpO2**
- **Maintain Blinding**

Evidence for Currently used SpO2 Ranges is Lacking

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.**

Variation in High and Low Alarm Limits in UK

Tin et al, Paediatric Respiratory Reviews 2003; 4:9-14



Hi Alarm

Low Alarm

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting these data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- 14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks
- Study performed to document practice prior to a trial with design parallel to SUPPORT
- Reported SpO2 limits ranged:
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- Median SpO2 in Hagadorn = 95%
- Median SpO2 from SUPPORT –
  - All infants in trial in any oxygen = 92% and 94%
  - Infants in Oxygen for full day = 91% and 93%
- Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.

Additional Evidence

Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%

- **Hagadorn study -**
  50% of the time with SpO2 > 95%
- **Case Western – Concurrent ELBW non-SUPPORT Infants - 51% time SpO2 > 95%**

Effects of Room Air on SpO2 > 95%

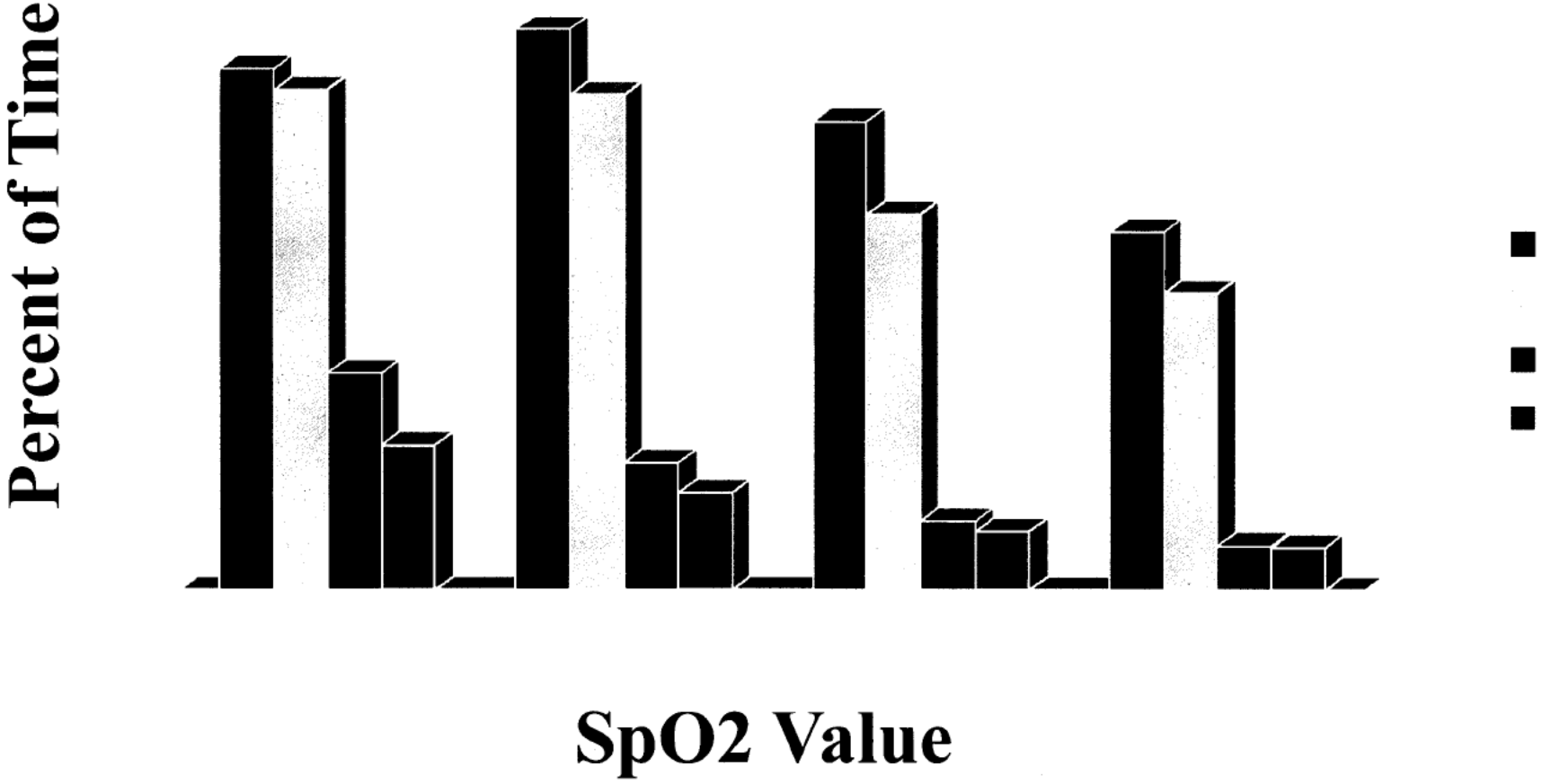
- **SUPPORT Infants on room air – SpO2 > 95% from 57% to 67% of time**
- **The Median SpO2 values while in Room air for the 91%-95% and 85%-89% Groups are 97% and 96%**
- **Median SpO2 in healthy preterm infants in room air = 97%**
  - **(Ng et al Arch Dis Child 1998;79:F64)**
- **Infants in room air can not have changes made to their inspired oxygen to lower their SpO2s.**

SpO2 values of SUPPORT infants in Room Air

Percent of Time Spent at $SpO_2 > 96\%$

	91%- 95% Group	85% - 89% Group
Room Air	51.7%	45.1%

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



The Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **These files can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Evaluation of SpO2 Information

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The magnitude of the effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Evaluation of SpO2 ranges

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- Analyses that incorrectly assigned infants on room air to be analyzed as receiving supplemental oxygen would overestimate saturations > 95%
- Initial analyses assigned infant to oxygen if given oxygen for any part of a day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.
- This incorrectly assigned some infants in RA for part of a day to the Oxygen analysis.

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.2%	13.5%
> 96%	14.1%	9.4%

SpO2 values of SUPPORT infants in Room Air

Percent of Time Spent at $SpO_2 > 96\%$

	91%- 95% Group	85% - 89% Group
Room Air	51.7%	45.1%
Oxygen	14.1%	9.4%

- Infants in room air had a > *three fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.

Safety Issue of SpO2 > 95% Summary - 1

- We believe that neither oximeter group in the SUPPORT trial is being exposed to greater durations of SpO2 > 95% while receiving oxygen than ELBW infants currently receiving usual care.
- Previous analyses overstated the exposure.
- Most of the overestimate was from misclassification of infants being assigned to oxygen but who received oxygen for only a part of a given day.

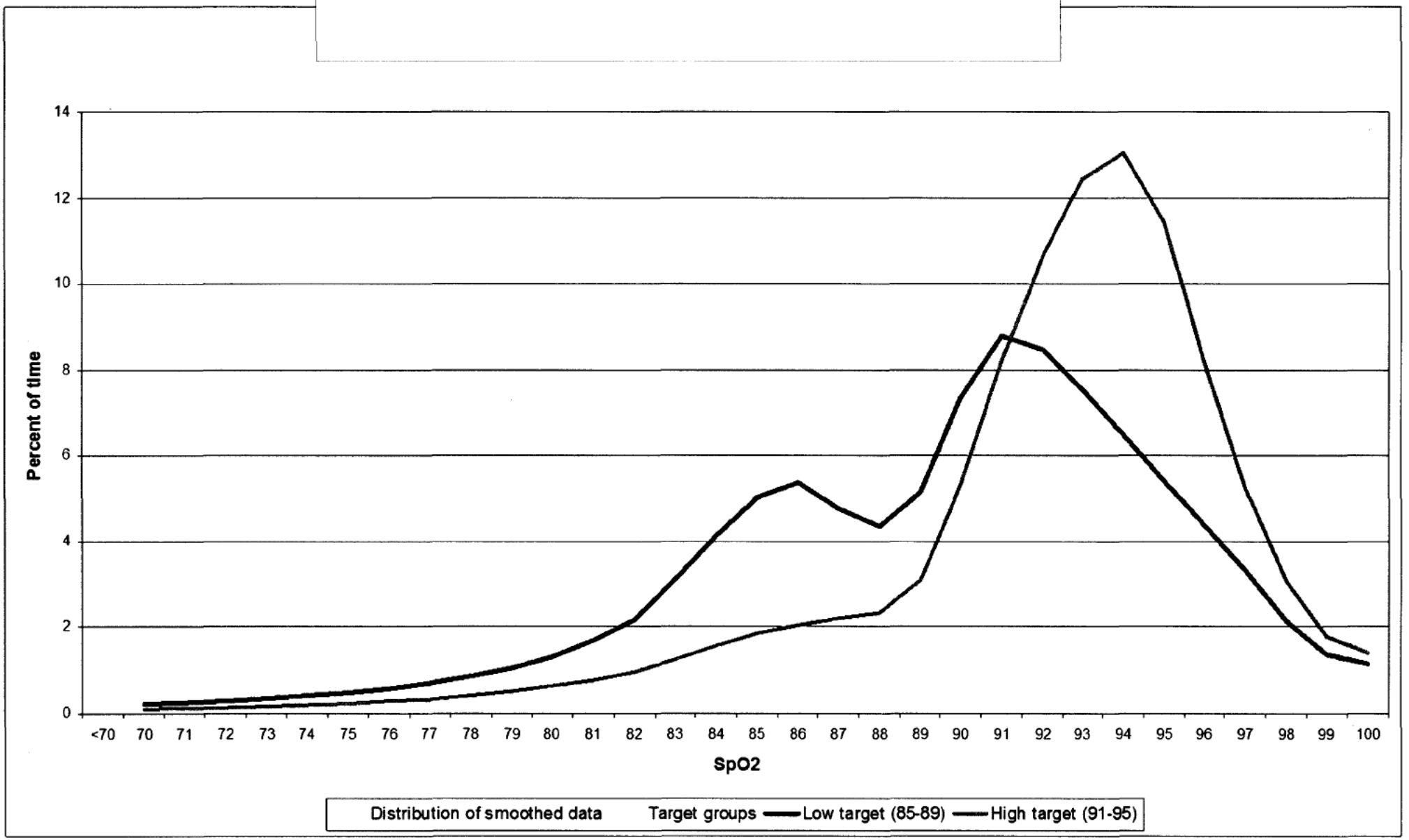
Safety Issue of SpO2 > 95% Summary - 2

- **This trial will help determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**
- **Current observations report a higher percent of SaO_2 > 95% than in the high target group in SUPPORT**

Futility Regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - **Mean - in any supplemental oxygen – 90% vs 92%**
  - **Median - in any supplemental oxygen – 92% vs 94%**
  - **Median - in oxygen at all 3 data points - 91% vs 93.5%**
- **Time with an SpO2 of ≤ 90% for infants in oxygen at all 3 data points shows a difference of > 25%**
  - **91% - 95% Group = 21.8%**
  - **85% - 89% Group = 47.1%**

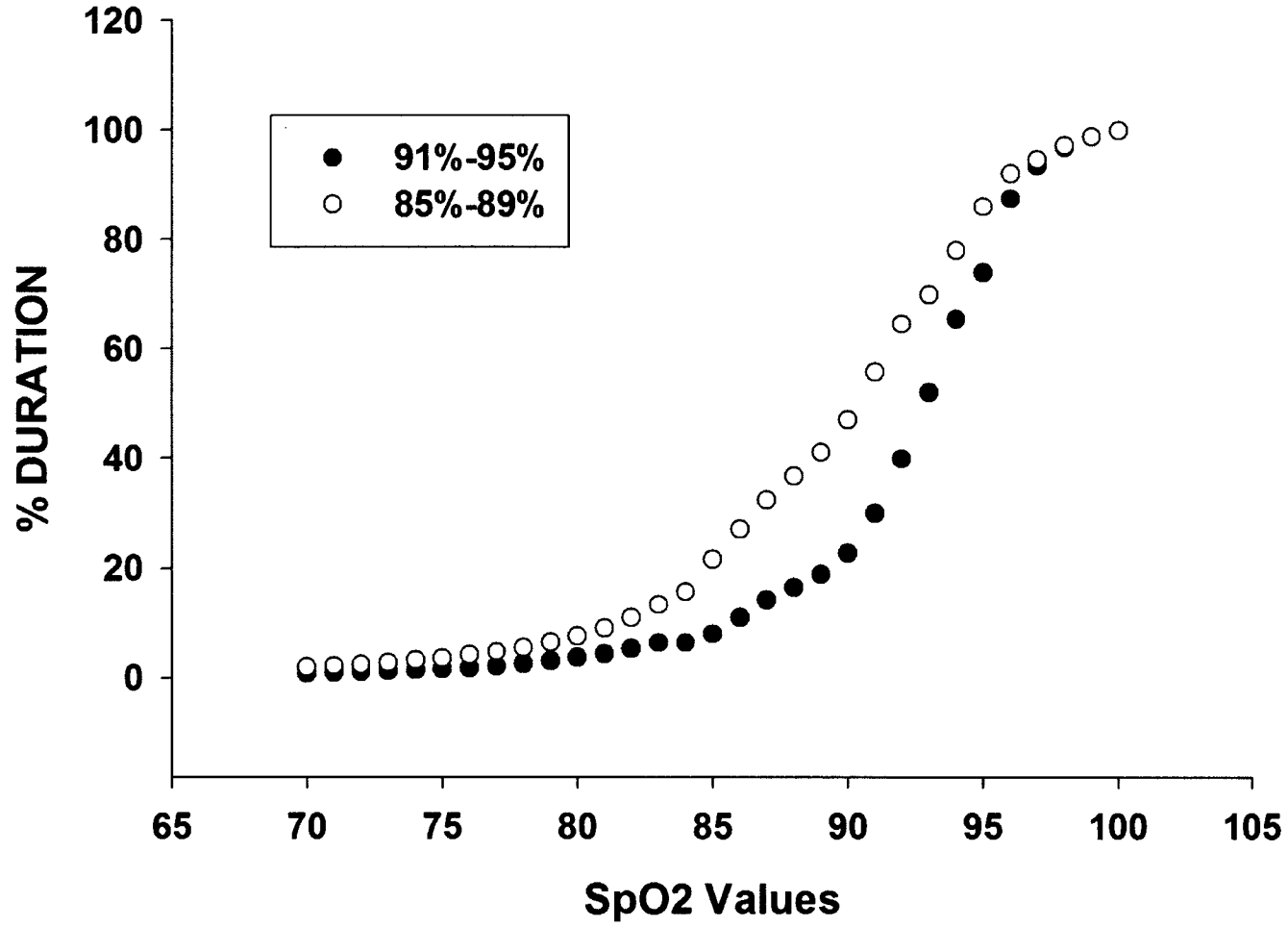
Based on Oxygen Days



Slide 27

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



Futility Regarding Separation of Oximeter Groups

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

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - **91%-95% group = 23%**
  - **85%-89% group = 35%**
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**
8. **Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.**

Conclusions

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

From: Neil Finer
To: "Das, Abhik"
Cc: "Wade Rich"; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer
Subject: RE: Site monitoring
Date: Thursday, January 26, 2006 11:17:10 AM

Hi Abhik
We have developed the following format for the site visits
Please review and suggest modifications as you see fit
Our template for this is the usual and customary practices of CRO's involved in FDA regulated research.
Regards
Neil and Wade

The purposes of these visits should be as follows:
To determine if the protocol being followed
To determine that the data being sent in are consistent with source documentation

Oximetry –
Was initial oximeter assigned to patient identical to the oximeter RTI has assigned to Patient
Are all alarms set properly and functioning.
Is labeling appropriate? (No visible color coding)
Are all study subjects who are on supp. oxygen on a study oximeter?
At the time of the visit, is the serial # of the oximeter the same as that which is documented ?

Ventilation
Site visit team to review Respiratory data sheet to determine if intubation/extubations followed protocol
DR – Time of surfactant administration – is it documented?

Documentation -
Informed consent signed and in the medical record?
All Inclusion criteria met, and no exclusions?
Random review of data on Supp05 and Supp11 for accuracy against source doc- most likely Respiratory data sheet
Do infants who reached 36 weeks have appropriate documentation of challenge, and was it done properly ?

Training -
Does staff know about the SUPPORT trial?
Is there visible indication of appropriate sat ranges?

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, January 26, 2006 6:40 AM
To: nfiner@ucsd.edu
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Site monitoring

Guys:

We are trying to come up with a list of activities to be performed as part of Network site monitoring visits and the expectations and requirements thereof. The site monitor(s) would check on both SUPPORT and other ongoing Network studies (mainly, GDB and FU). Please let me know what specific activities/expectations you would have for a site monitor with respect to SUPPORT.

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: Wade Rich
To: "Das, Abhik"; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Site monitoring
Date: Thursday, January 26, 2006 9:54:56 AM

I guess this is a bizarre question to ask after nearly 5 years, but do we define what the source doc. is for our data collection, or just use the generic "medical record" ? This comes up because in order to monitor a site, we would need to know what source contains the truth. If an FiO2 of .21 is written on the Supp05, and the respiratory flow sheet shows .25 and the nursing flow sheet shows .22, we need to know which is the acceptable source. If we are only checking to see that what is on the written chart is what ended up in the data input, we are only checking on the data entry, not the correctness of the data.
Wade

From: Das, Abhik [mailto:adas@rti.org]
Sent: Thursday, January 26, 2006 6:40 AM
To: nfiner@ucsd.edu
Cc: Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Site monitoring

Guys:

We are trying to come up with a list of activities to be performed as part of Network site monitoring visits and the expectations and requirements thereof. The site monitor(s) would check on both SUPPORT and other ongoing Network studies (mainly, GDB and FU). Please let me know what specific activities/expectations you would have for a site monitor with respect to SUPPORT.

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: Avroy A. Fanaroff
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Support
Date: Wednesday, January 25, 2006 6:43:47 PM

Apologies accepted
I assumed it was an oversight- which you have confirmed
This has been an interesting exercise and we have all learned a lot - hopefully it will make our future trials even more robust
We must also appreciate the process - this is all part of research today and the DSMC is to be congratulated for protecting our subjects when they thought they were at risk and revising their stand when presented with the potent data that we had collected during the trial.
Best wishes
Av

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

From: Higgins, Rosemary (NIH/NICHD) [E]
Date: 01/25/06 18:26:22
To: aaf2@po.cwru.edu
Subject: Re: Support

Av
Please accept my apologies. I am so sorry to have left you off the email list.
Thanks for your kind comments.
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Avroy A. Fanaroff <aaf2@pop.cwru.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Wed Jan 25 18:17:29 2006
Subject: Support

Hi Rose
Congratulations
I am delighted with the outcome
Please not that I was not on your E mail list despite still being a member of the subcommittee
regards
Avroy

The enclosed information is STRICTLY CONFIDENTIAL and is intended for the use of the addressee only. The University Hospitals Health System and its affiliates disclaim and responsibility for unauthorized disclosure of this information other then the addressee.

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR 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.

The enclosed information is STRICTLY CONFIDENTIAL and is intended for the use of the addressee only. The University Hospitals Health System and its affiliates disclaim and responsibility for unauthorized disclosure of this information other then the addressee.

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR 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: Wade Rich
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Hastings, Betty J."; "Neil Finer"
Subject: Changes
Date: Wednesday, January 25, 2006 2:19:21 PM
Attachments: OXYGEN WITH LOVEAppendix.doc
DSMC Restart Lettert.doc
SUPPORT Protocol Updated01_25_06.doc

Rose, Betty,
Here are the owl appendix, a letter, and the protocol with changes. I am not sure where these training issues would go in the manual. The only thing I see should be in there is the change to the data collection form when we decide on FiO2 frequency and the two appendices, OWL and the one from Case. Your thoughts?
wade

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

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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

The DSMC for the NICHD Neonatal Research Network SUPPORT trial met with the principle investigator and data management team on January 24th 2005 in Washington D.C. After reviewing the data presented the committee agreed to restart the trial. (See attached letter) This was based on the implementation of the following changes presented to the committee by Dr. Neil Finer as representative of the SUPPORT subcommittee:

1. Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours
2. Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air. (Section 7.1)
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 84% and 96%. We will train sites based on the OWL (Oxygen with Love) program developed at Oschner. (Section 6.1.2 and Appendix 1)
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation. (Section 6.1.2 and Manual Appendix XX)
5. Place bedside cards to indicate the desired target range.
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites. (6.1.2)
7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.
9. ? High Sat Alarms

The items listed above which are relevant to the protocol have been changed in the attached version and highlighted.

Thank you for providing an expedited review of these minor changes to the protocol and allowing us to renew enrollment in this important study.

Sincerely,

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
Updated March 28, 2005

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 ≥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, air leak)

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
- 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 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.

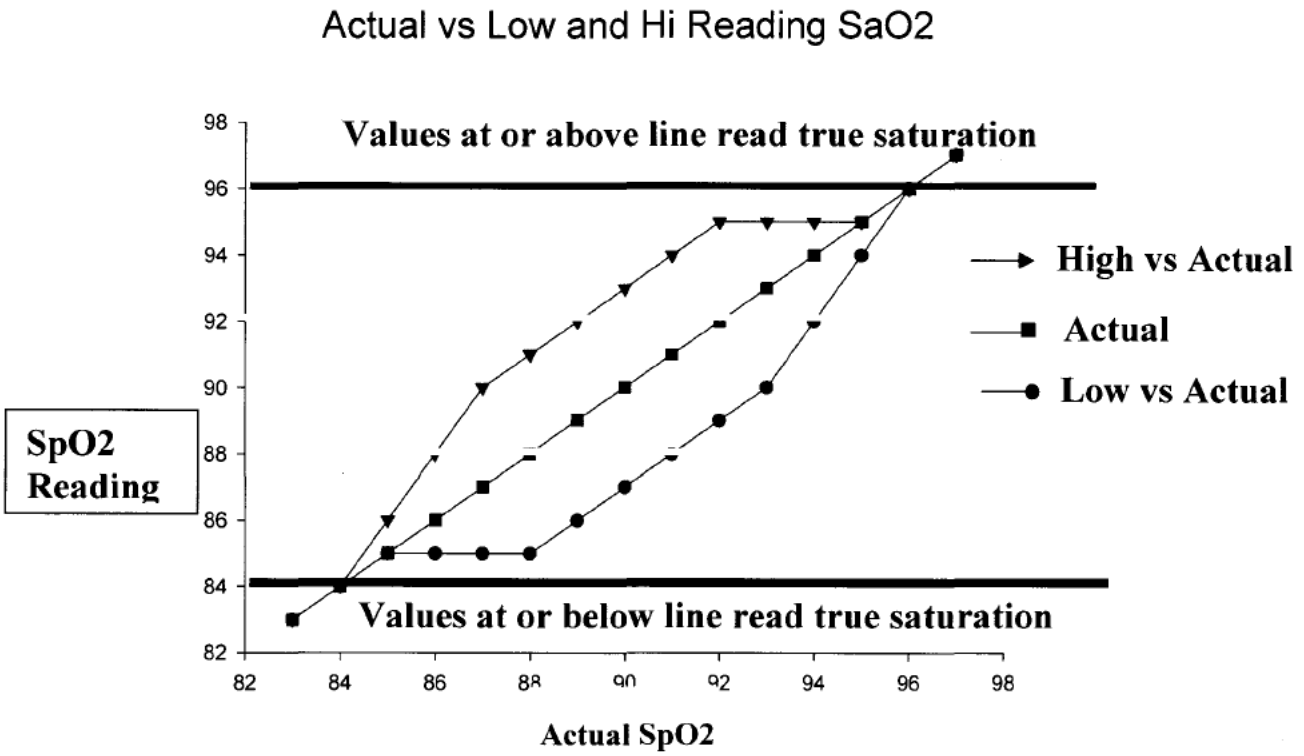
The suggested alarms limits will be 84% and 96% for both groups.

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.

Training will be repeated during the trial which will include suggestions on how to manage desaturation events, and assistance in implementing a program for maintaining

saturation levels based on the Oxygen With Love (OWL) protocol. (See Appendix X Training Manual)

RTI will coordinate random site visits to monitor and review compliance with the protocol.

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.

FiO2 data will be collected ____ times per day in the first 14 days of life to ensure that we are only analyzing data during supplemental oxygen administration when adjustment of FiO2 is possible.

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

		Low	High	Overall
CPAP	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

		Low	High	Overall
CPAP	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

		Low	High	Overall
CPAP	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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Hi
Date: Monday, January 23, 2006 8:33:20 PM

Good. I know them all.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Mon Jan 23 19:31:34 2006
Subject: Re: Hi

There are also three ad hoc members for the SUPPORT trial. They are:
Merrin Thomsom (from Hammersmith),
Carl Hunt (NhLBI), and
Marilee Allen (Neo fromHopkins with FU expertise).
Sorry I didn't include them in the first email.

Thanks again
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Mon Jan 23 20:23:24 2006
Subject: Re: Hi

Rose
Good. I know Bob, tracy and Marian. See you tomorrow.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Mon Jan 23 19:18:02 2006
Subject: RE: Hi

Wally
The other members are:
Robert Boyle (neonatologist and ethicist at Univ of Virginia)
Carol Redmond - biostatistics
Traci Clemons - biostatistics
Mary D'Alton - MFM
Marian Willinger - NICHD member - she has many of teh SIDS grants and control of breathing studies in the Pregnancy and Perinatology branch.

Hope this helps!
Rose

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Mon 1/23/2006 8:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Hi

Rose: thanks a lot. I do not have a list of the members of the DSMB. I know Gordon and Chris. Who are the other neonatologists?
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
Sent: Mon Jan 23 18:36:39 2006
Subject: Re: Hi

Thanks
Let me know if you need anything. I will be in the office between 7:30-7:45 am.
Take care
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Jan 23 19:23:24 2006
Subject: Re: Hi

Hi. Rose. I just arrived. I will meet with Neil tonight or in the morning depending if he is late or not.
Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Jan 23 17:07:06 2006
Subject: Hi

Hi,
I hope your trips were uneventful. If you need to reach me, my home number is 703-827-(b) (6), cell 703-395-(b) (6) and office 301-435-7909.

See you tomorrow and THANKS

Rose

Sent from my BlackBerry Wireless Handheld

From: Neil Finer
To: "Zaterka-Baxter, Kristin"
Cc: "Carlo Waldemar (E-mail)"; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: DSMC Support mtg.
Date: Sunday, January 22, 2006 3:56:56 PM

Hi Kristen
Will you ensure that there is a projector at the DSMC meeting?
Many thanks
Neil Finer

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, January 20, 2006 7:43 AM
To: Neil Finer
Cc: Gantz, Marie
Subject: RE: DSMC Support mtg.

Attached,..

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From: Zaterka-Baxter, Kristin
Sent: Friday, January 20, 2006 10:42 AM
To: 'Neil Finer'
Cc: Gantz, Marie
Subject: RE: DSMC Support mtg.
Importance: High

One more thing Marie noticed in changing these percentages; on slide 24 (in red). She said it's not a big deal and is correct however, if we change the percentage to 25% instead of 24% it makes a stronger case.
Please let me know.
Thanks again,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, January 20, 2006 10:13 AM
To: Zaterka-Baxter, Kristin

Cc: Gantz, Marie; Hastings, Betty J.; wrich@ucsd.edu; wcarlo@peds.uab.edu; 'Neil Finer'
Subject: RE: DSMC Support mtg.

Hi Kristin and Marie
I have made all of Marie's changes. I had not made the decimal point changes and I have now used all of her data.
I have attached the revised file
Thanks
Neil

-----Original Message-----
From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Friday, January 20, 2006 6:52 AM
To: nfiner@ucsd.edu
Cc: Gantz, Marie; Hastings, Betty J.; wrich@ucsd.edu; wcarlo@peds.uab.edu
Subject: RE: DSMC Support mtg.
Importance: High

Hi Dr. Finer,
Betty mentioned this morning that you and Marie Gantz we looking into some of the data for your presentation yesterday so I sent this to her to review. She had a few comments on slide 14, 21 and 24 regarding the percentages based on the latest analysis and on slide 21 regarding the date of analysis. These comments are in red on each slide. Please take a look and let me know what you would like to proceed. Marie's contact info is below incase you have any questions.
Thanks,
Kris

Marie Gantz: 919-485-7780
mgantz@rti.org

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kzaterka@rti.org

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 19, 2006 6:44 PM
To: Zaterka-Baxter, Kristin
Cc: 'Wally Carlo, M.D.'; 'Higgins, Rosemary (NIH/NICHD) [E]'; wrich@ucsd.edu
Subject: RE: DSMC Support mtg.

Hi Kristin
Would you make handouts from the attached presentation to be given to the DSMC members? It looks best as 3 slides per page I will follow this framework and they will be able to follow and make notes as we discuss.
Many thanks
Neil

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 19, 2006 10:10 AM

To: nfiner@ucsd.edu
Cc: fmartinez@ucsd.edu; Hastings, Betty J.; Petrie, Carolyn; Das, Abhik
Subject: DSMC Support mtg.

Dr. Finer,

What hard copy materials, if any, would you like available to the DSMC members during your presentation on the 24th

Thanks,

Kris Zaterka-Baxter, RN, BSN, CCRP
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Statistics and Epidemiology
4426 South Miami Blvd.
Durham, NC 27703
Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT - DSMC Response
Date: Friday, January 20, 2006 10:15:47 AM

Hi Rose
You are very kind and thoughtful.
Interesting how the very young and very old seem to sleep less.
Enjoy your family!
See you Tuesday
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2006 7:11 AM
To: Neil Finer
Subject: RE: SUPPORT - DSMC Response

I was going to offer you dinner at our chaotic home, but (b) (6) [redacted]
Take care
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, January 20, 2006 10:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT - DSMC Response

Hi Rose
I sent a handout file without the additional slides that I kept for questions.
I will be arriving Monday evening at 8:30 PM so I assume that I would be at the Hotel before 10:00 PM.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2006 5:25 AM
To: nfiner@ucsd.edu
Subject: RE: SUPPORT - DSMC Response

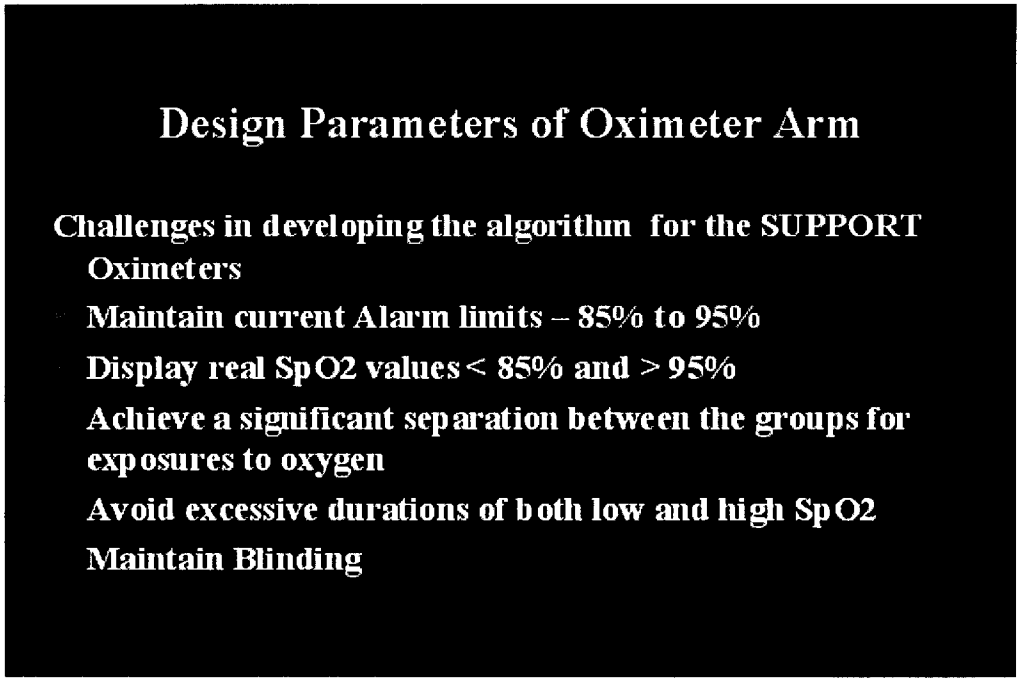
Neil
I assume this was in the file sent to Kris for distribution. This is fine.

Also when will you arrive for the meeting?
Thanks
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, January 18, 2006 12:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wade Rich
Subject: RE: SUPPORT - DSMC Response

Thanks Rose
I am going to add one more slide as I believe we need to share with the DSMC our reasons for the development of the algorithm. I have pasted it below for you. It will be slide #7

Do you want me to send a version of this to the DSMC? They currently all have the data and presentations that we sent them for the Dec meeting. This presentation is more condensed, but I think that if they have reviewed what we sent them, we should be able to present this to them without pre-circulating it.
I think that my preference is not to send this, as I will probably want to tweak till the last moment.
I think we have set the correct tone, and presented the data in an appropriate fashion.
Thanks for your input
Regards
Neil



-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
[mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 18, 2006 3:32 AM
To: Neil Finer
Subject: RE: SUPPORT - DSMC Response

Neil
I could open this one and have gone over the slides. I believe you have captured the essence of the points discussed at the steering committee meeting. The only suggestion I have - for in "in oxygen," should we say "supplemental oxygen?" It is very minor, but may help with the RA versus oxygen issue. - I leave it up to you.
Thank you for all the of effort, hard work and dedication!
Rose

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tue 1/17/2006 11:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT - DSMC Response

Hi Rose

Let me know if you can open this

Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 17, 2006 5:07 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; Das, Abhik; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject: SUPPORT - DSMC Response

Hi All

I have incorporated the suggestions from Michele, Wally, Ed, and Shahnaz and added some new info. The overall presentation is 33 slides, with 2 additional that I would keep for questions. The first 2 slides are the DSMCs recommendations and the next 2 are our Summary, and the final one takes no time.

Slide 12 - I believe is important as it points out our actual Median values in Room air which are the same as those previously reported, and the problem with being in room air - that you cannot alter the infants SpO2.

Marie sent new data that I requested, and I have not made any changes as a result as the values are so close. This does provide more confidence in our analyses.

I have made slight editorial changes. Please review and let me know your thoughts.

Neil

From:	Neil Finer
To:	"Zaterka-Baxter, Kristin"
Cc:	"Wally Carlo, M.D."; Higgins, Rosemary (NIH/NICHD) [E]; wrich@ucsd.edu
Subject:	RE: DSMC Support mtg.
Date:	Thursday, January 19, 2006 6:44:33 PM
Attachments:	DSMC Jan 18 - Handout.ppt

Hi Kristin
Would you make handouts from the attached presentation to be given to the DSMC members? It looks best as 3 slides per page I will follow this framework and they will be able to follow and make notes as we discuss.
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Sent: Thursday, January 19, 2006 10:10 AM
To: nfiner@ucsd.edu
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Subject: DSMC Support mtg.

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kzaterka@rti.org

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 24, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became markedly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by 12% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- **The optimal saturation range for ELBW is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Design Parameters of Oximeter Arm

Challenges in developing the algorithm for the SUPPORT Oximeters

- Maintain current Alarm limits – 85% to 95%
- Display real SpO2 values < 85% and > 95%
- Achieve a significant separation between the groups for exposures to oxygen
- Avoid excessive durations of both low and high SpO2
- Maintain Blinding

Evidence for Currently used SpO2 Ranges is Lacking

- SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.
- Prior to the initiation of this study not all centers always used a high SpO2 alarm.
- Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting these data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- **14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks**
- **Study performed to document practice prior to a trial with design parallel to SUPPORT**
- **Reported SpO2 limits ranged:**
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- **Median SpO2 in Hagadorn = 95%**
- **Median SpO2 from SUPPORT –**
  - All infants in trial in any oxygen = 92% and 94%
  - Infants in Oxygen for full day = 91% and 93%
- **Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.**

Additional Evidence

Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%

- **Hagadorn study -**
  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants -**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW non-SUPPORT infants - 51% time SpO2 > 95%**

Effects of Room Air on SpO2 > 95%

- **SUPPORT Infants on room air – SpO2 > 95% from 57% to 67% of time**
- **The Median SpO2 values while in Room air for the 91%-95% and 85%-89% Groups are 97% and 96%**
- **Median SpO2 in healthy preterm infants in room air = 97%**
  - **(Ng et al Arch Dis Child 1998;79:F64)**
- **Infants in room air can not have changes made to their inspired oxygen to lower their SpO2s.**

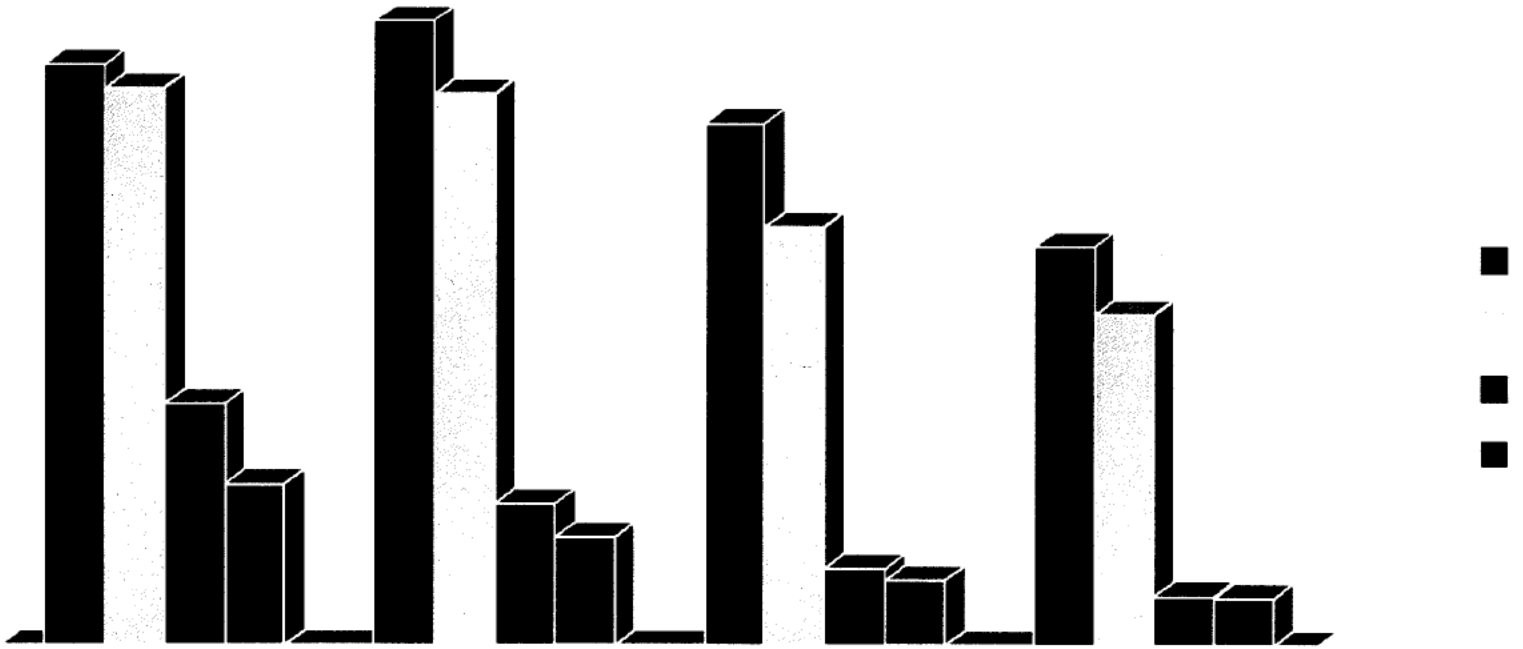
SpO2 values of SUPPORT infants in Room Air

Percent of Time Spent at $SpO_2 > 96\%$

	91%- 95% Group	85% - 89% Group
Room Air	52.7%	46.1%
Oxygen	14%	9.4%

- Infants in room air had a > *three fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



The Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **These files can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Evaluation of SpO2 Information

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Evaluation of SpO2 ranges

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- **Analyses that incorrectly assigned infants on room air to be analyzed as receiving supplemental oxygen would overestimate saturations > 95%**
- **Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.**
- **This incorrectly assigned some infants in RA for part of a day to the Oxygen analysis.**

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.2%	13.5%
> 96%	14%	9.4%

Safety Issue of SpO2 > 95% Summary - 1

- We believe that neither oximeter group in the SUPPORT trial is being exposed to greater durations of SpO2 > 95% while receiving oxygen than ELBW infants currently receiving usual care.
- Previous analyses overstated the exposure.
- Most of the overestimate was from misclassification of infants in oxygen for part of a day.

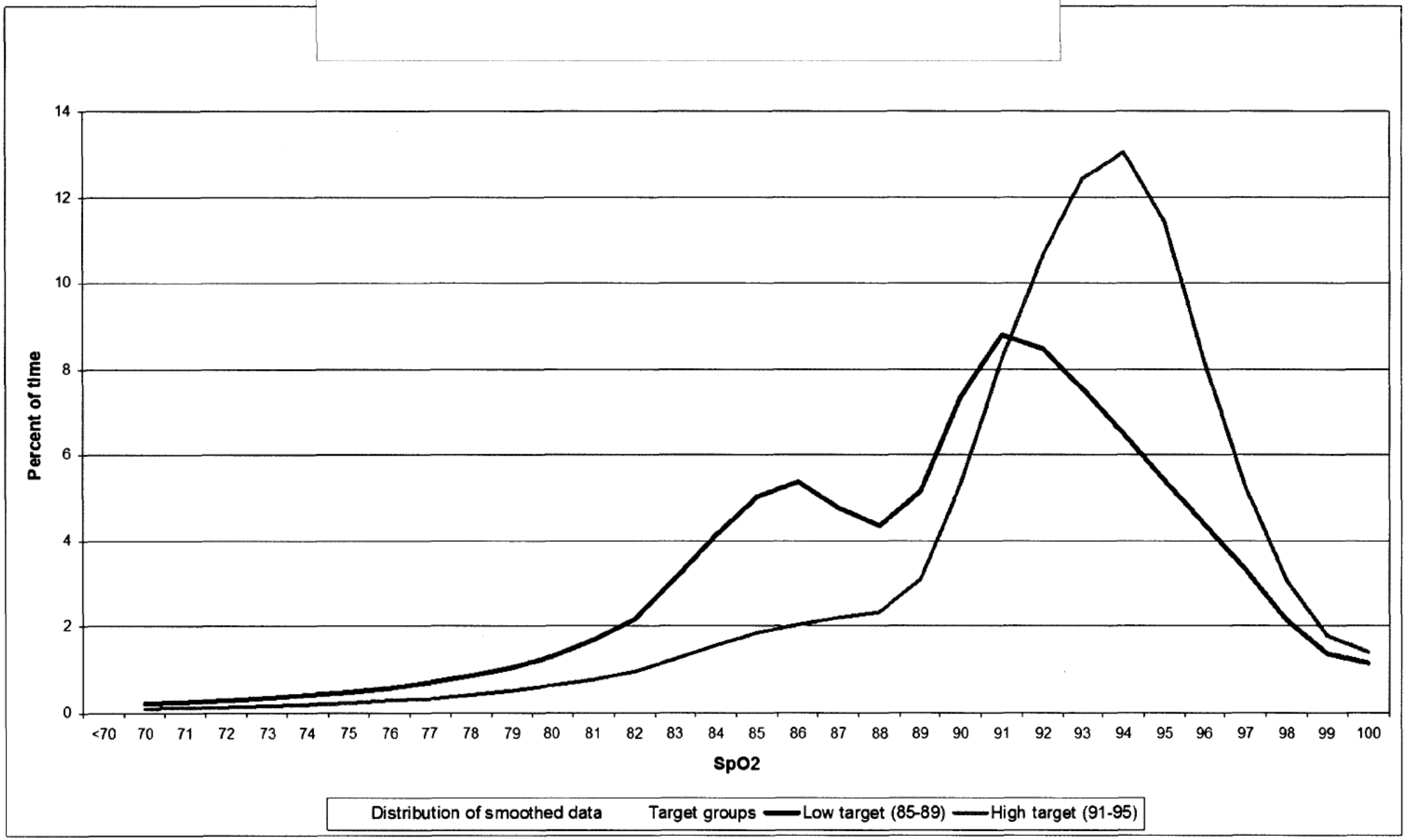
Safety Issue of SpO2 > 95% Summary - 2

- **This trial will help determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**
- **Similar small studies report a higher percent of SaO_2 > 95% than in the high target group in SUPPORT**

Futility Regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - **Mean - in any supplemental oxygen – 90% vs 92%**
  - **Median - in any supplemental oxygen – 92% vs 94%**
  - **Median - in oxygen at all 3 data points - 91% vs 93.5%**
- **Time with an SpO2 of ≤90% for infants in oxygen at all 3 data points shows a difference of > 24%**
  - **91% - 95% Group = 22.8%**
  - **85% - 89% Group = 47.6%**

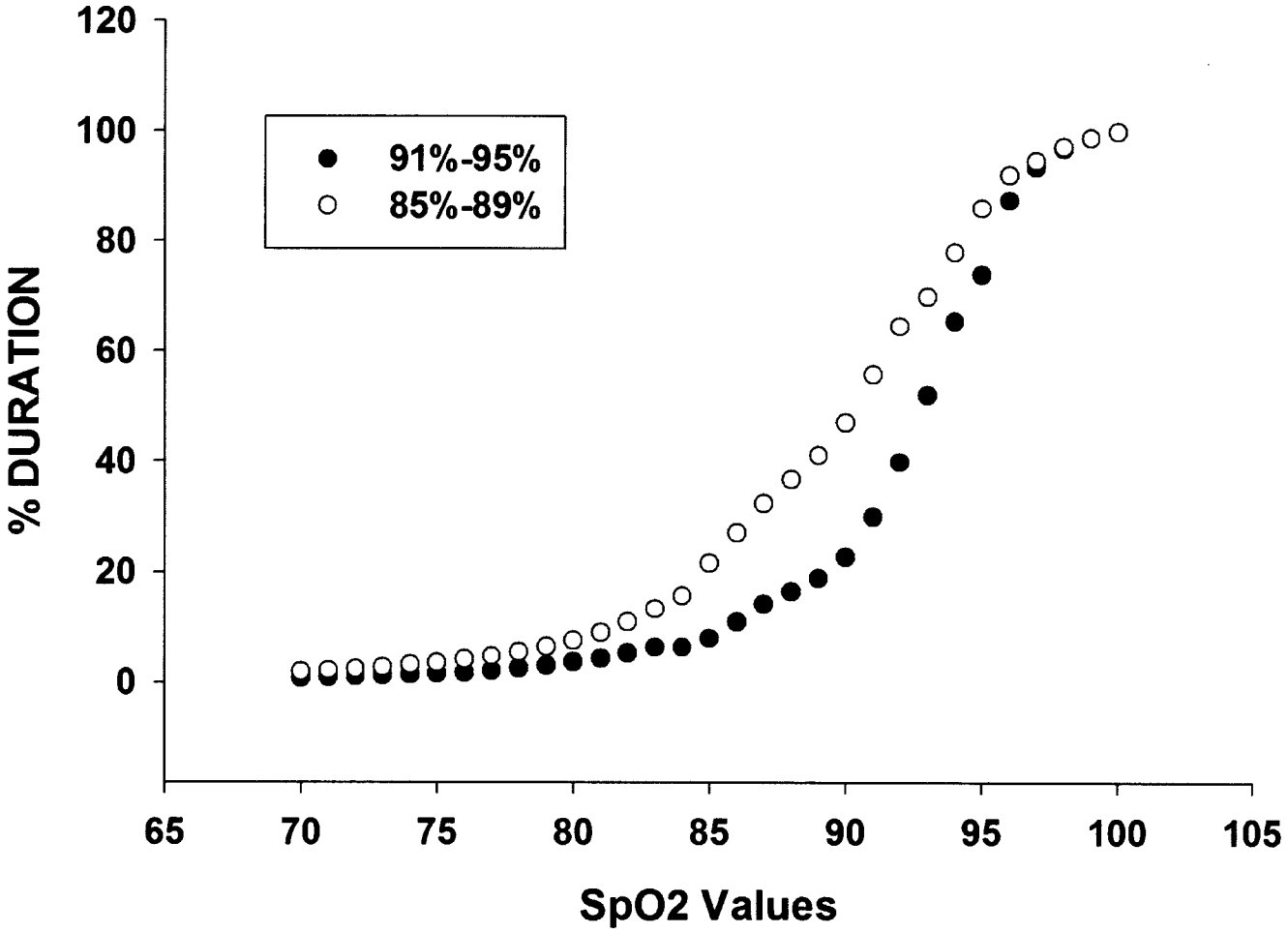
Based on Oxygen Days



Slide 25

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



Futility Regarding Separation of Oximeter Groups

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

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - **91%-95% group = 23%**
  - **85%-89% group = 35%**
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**
8. **Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.**

Conclusions

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

From:	Wally Carlo, M.D.
To:	Duara, Shahnaz; nfiner@ucsd.edu; mcw3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]; Edward.Donovan@cchmc.org; wrich@ucsd.edu; Nxs5@po.cwru.edu
Cc:	Wally Carlo, M.D.
Subject:	RE: Updated DSMC slides
Date:	Wednesday, January 18, 2006 11:28:19 AM
Attachments:	DSMC Jan 17 revised.ppt

Dear all:
I have made the following changes directly to the slides.

Slide #4: Under bullet 2 - made the "o" in oxygen lowercase. Bullet 3 - changed the word "significantly" to "markedly".

Slide # 8: In the 4th bullet, first line - changed "this" to "these" data. . . .

Slide #12: Changed the bullets from "x" to "*". Moved (Ng et al Arch Dis Child 1998;79:F64) to second level bullet position.

Slide #13: Added the subtitle "Percent of Time Spent at SPO2 > 96%". Moved the paragraph "Infants in room air.... to the end of the page".

Slide # 21: Added the subtitle: Summary - 1

Slide #22: Added the subtitle: Summary 3. Deleted the word "to" in the first line. Added a bullet at the end that reads: "Similar small studies report a higher percent of SaO2 > 95% than in the high target group in SUPPORT.

Slide #32: Aligned paragraphs on the left.

Slide #33: Added "s" to Conclusion

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 24, 2006

Report of the DSMC Nov 2005

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Room Air	52.7%	46.1%
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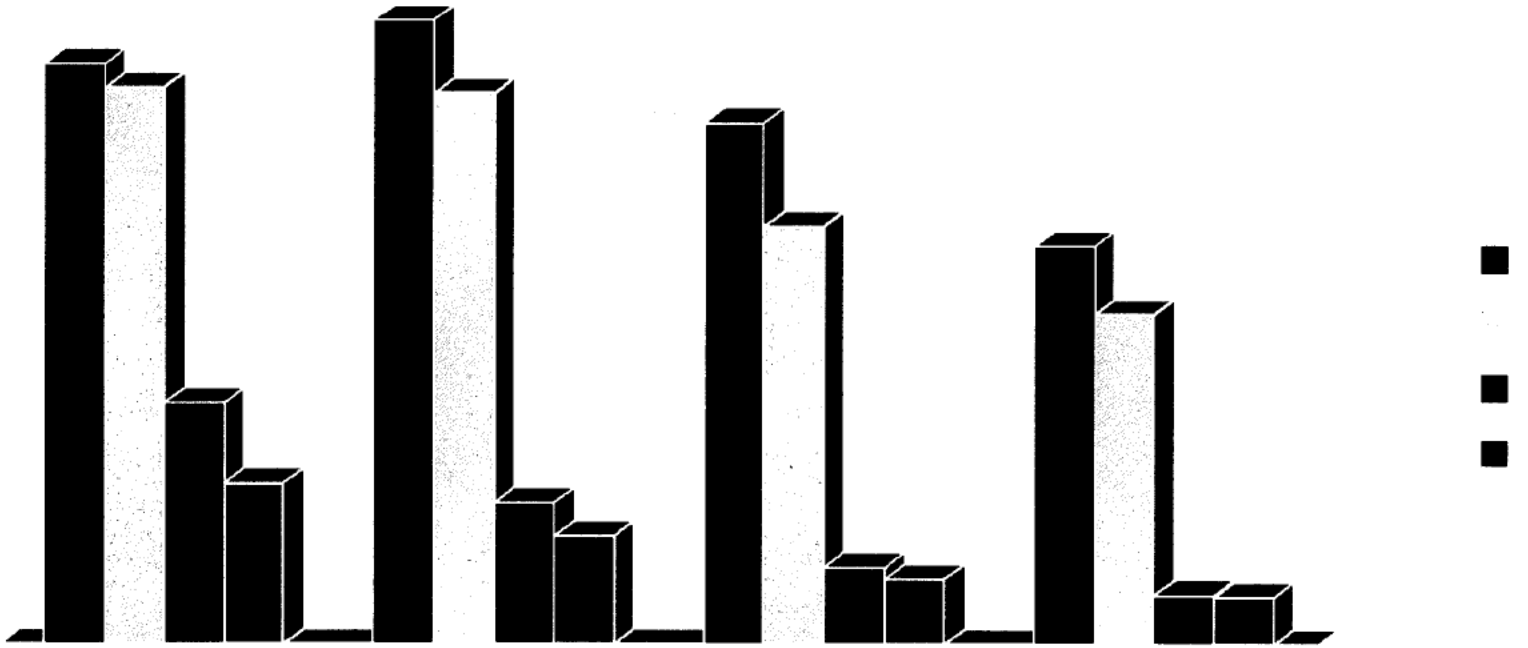

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Impact of including infants in oxygen for portion of day

- Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%
- Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.
- This incorrectly assigned some infants in RA to the Oxygen analysis.

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Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95% Summary - 1

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to greater durations of SpO2 > 95% while receiving oxygen than ELBW infants currently receiving usual care.**
- **Previous analyses overstated the exposure.**
- **Most of the overestimate was from misclassification of infants in partial oxygen.**

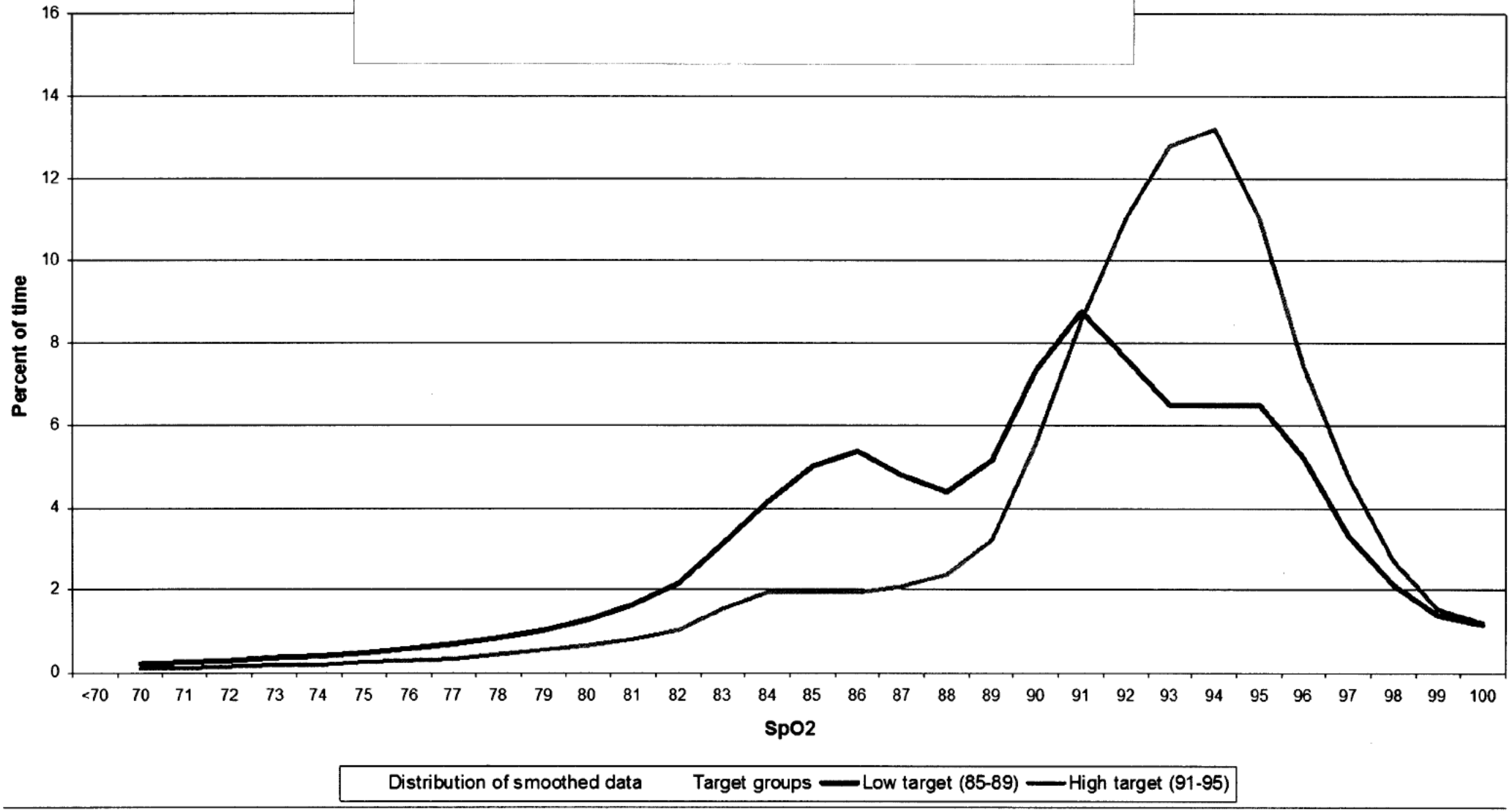
Safety Issue of SpO2 > 95% Summary - 2

- **This trial will help determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**
- **Similar small studies report a higher present of SaO_2 > 95% than in the high target group in SUPPORT**

Futility Regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - **Mean all infants – 90% vs 92%**
  - **Median all infants – 92% vs 94%**
  - **Median infants in oxygen at all 3 data points - 91% vs 93%**
- **Time with an SpO2 of ≤90% shows a difference of > 24%**
  - **91% - 95% Group = 22.8%**
  - **85% - 89% Group = 47.6%**

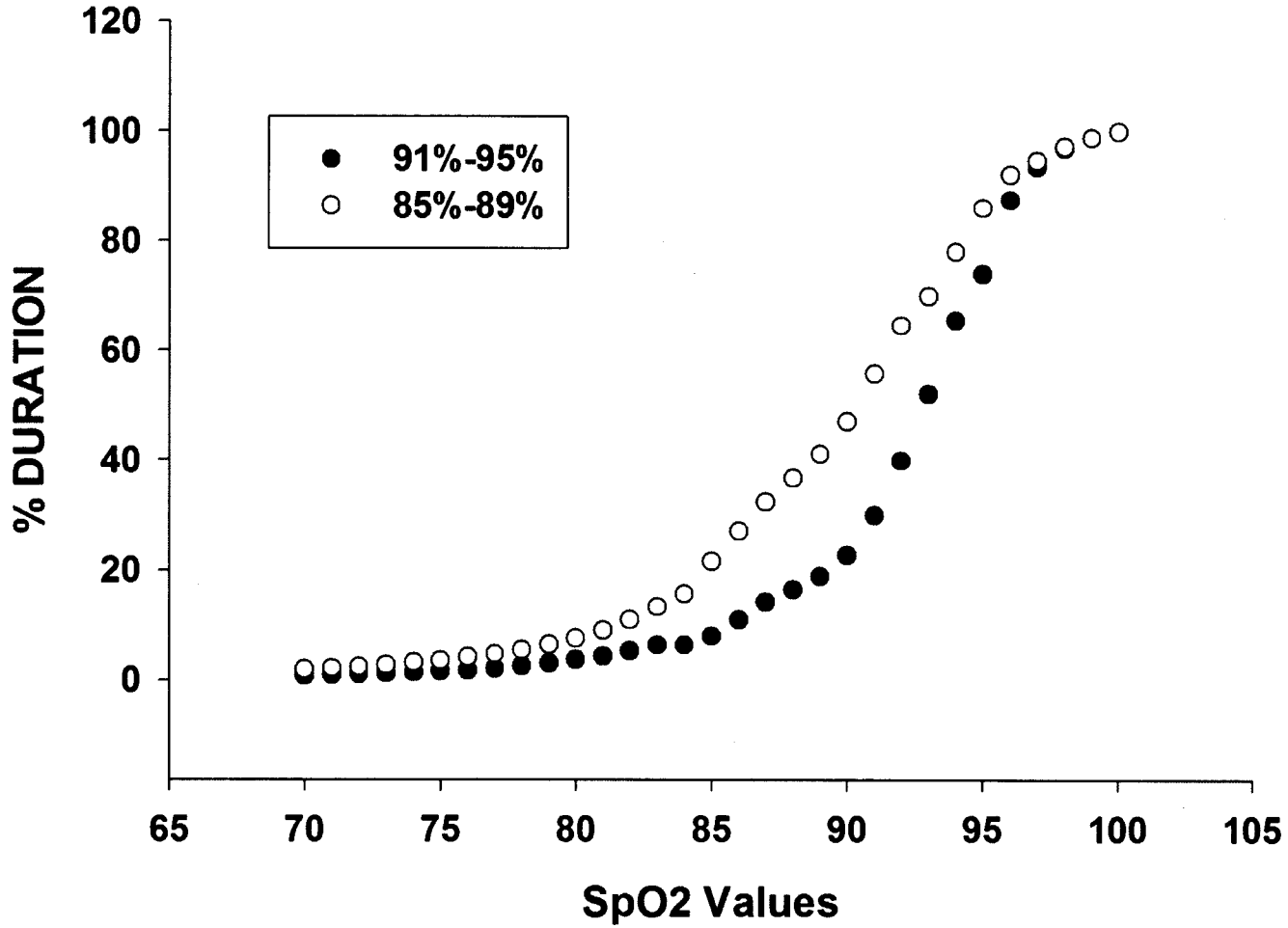
Based on Oxygen Days



Slide 24

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



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- 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 requirements between the groups

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - **91%-95% group = 26.6%**
  - **85%-89% group = 35.5%**
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

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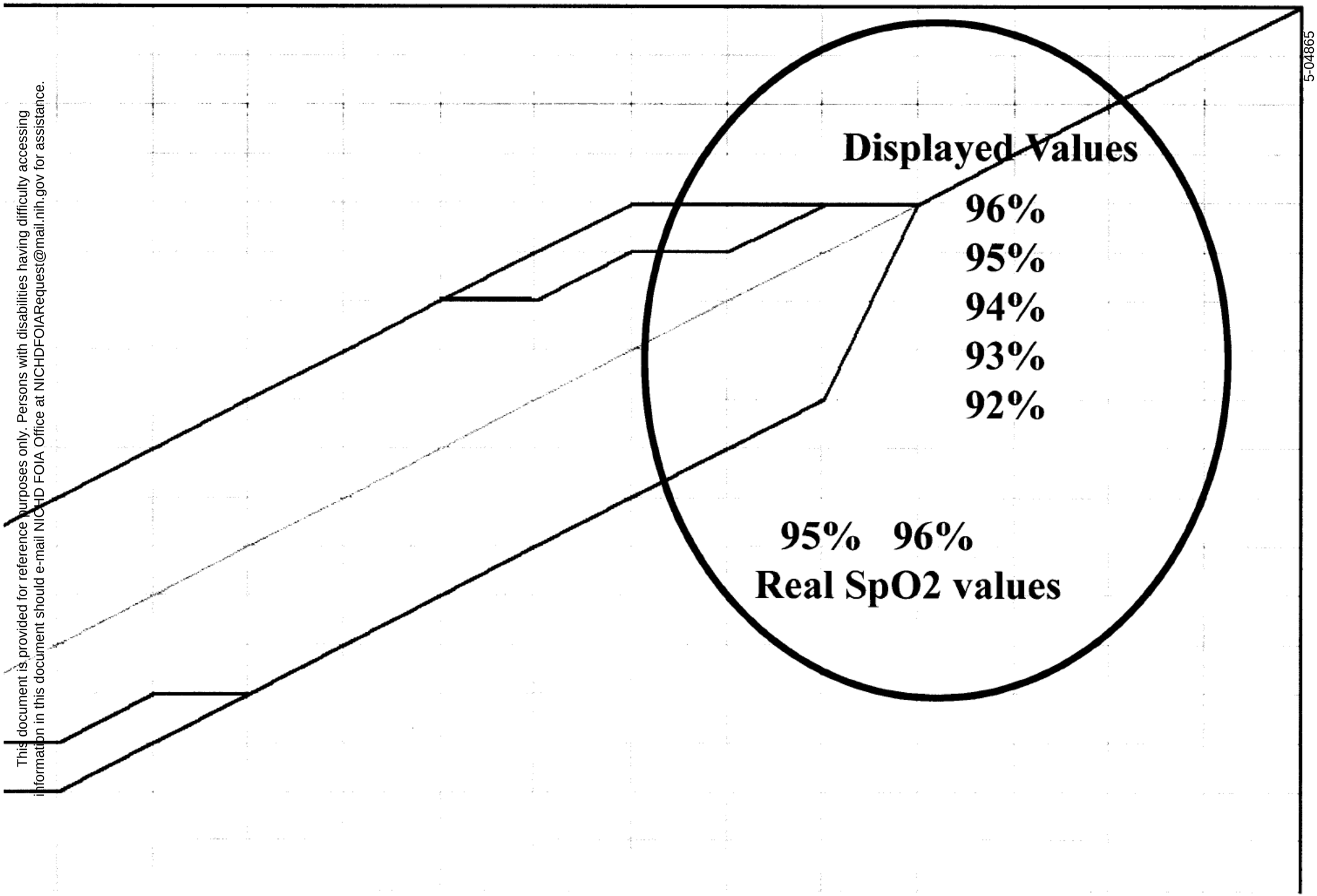
7. **Reanalyze group differences after an additional 100-150 infants have been enrolled.**
8. **Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.**

Conclusions

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

SpO2 Algorithm

- These SpO2 values represent an overlap of altered and real values of the SUPPORT SpO2 algorithm
- All displayed SpO2 values in SUPPORT > 96% and < 84% represent the actual unaltered SpO2
- Therefore, subsequent data will be presented for values > 96% and < 84%, rather than the expected >95% and <85%



From: Duara, Shahnaz
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; Wade Rich; Wally Carlo
Subject: RE: SUPPORT - DSMC Response
Date: Wednesday, January 18, 2006 11:22:33 AM

Hi Neil,

If you feel that 20 minutes will be sufficient to cover all the slides, I'm OK with this version. Slide18 is really important to go slow with as understanding it will be crucial to appreciating the impact of oxygen given for a portion of the day.

Shahnaz

> -----Original Message-----
> **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> **Sent:** Tuesday, January 17, 2006 8:07 PM
> **To:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; Das, Abhik; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
> **Subject:** SUPPORT - DSMC Response
>
> Hi All
> I have incorporated the suggestions from Michele, Wally, Ed, and Shahnaz and added some new info. The overall presentation is 33 slides, with 2 additional that I would keep for questions. The first 2 slides are the DSMCs recommendations and the next 2 are our Summary, and the final one takes no time.
> Slide 12 - I believe is important as it points out our actual Median values in Room air which are the same as those previously reported, and the problem with being in room air – that you cannot alter the infants SpO2.
> Marie sent new data that I requested, and I have not made any changes as a result as the values are so close. This does provide more confidence in our analyses.
> I have made slight editorial changes. Please review and let me know your thoughts.
> Neil

From: Duara, Shahnaz
To: Wally Carlo, M.D.; nfiner@ucsd.edu; mcw3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]; Edward.Donovan@cchmc.org; wrich@ucsd.edu; Nxs5@po.cwru.edu
Subject: RE: Updated DSMC slides
Date: Tuesday, January 17, 2006 9:43:51 AM
Attachments: DSMC Jan 17 2006SD suggestions.ppt

Hi Neil,

I think it's fine to handle the 94% issue the way you plan. I have looked through the slides after Michelle's edits, and like the flow. The one place where I thought we needed explanation up front is where we go from the Hagadorn, STOP-ROP and Case data in slide # 13, all describing SpO2 time > 95%, to SUPPORT data in the next few slides illustrating times spent >96 %, without a clear explanation for why we elect to discuss > 96%. To clarify the switch, I inserted a new slide # 14 to make things clear up front- see if you think it helps.

As for the legends of Hercules, I'm not sure which task this whole business falls under - cleaning the stables?

Shahnaz

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, January 16, 2006 8:15 PM
To: nfiner@ucsd.edu; mcw3@case.edu; higginsr@mail.nih.gov; Edward.Donovan@cchmc.org; Duara, Shahnaz; wrich@ucsd.edu; Nxs5@po.cwru.edu
Subject: Re: Updated DSMC slides

I think they may ask questions about this either way but will be ok with not changing it.
Wally

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: 'Michele Walsh' <mcw3@case.edu>; 'Higgins, Rose' <higginsr@mail.nih.gov>; 'Donovan, Edward (DONOVAEF)' <edward.donovan@cchmc.org>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; 'Duara, Shahnaz' <SDuara@med.miami.edu>; 'Rich, Wade' <wrich@ucsd.edu>; 'Newman, Nancy' <nxs5@po.cwru.edu>
Sent: Mon Jan 16 18:52:41 2006
Subject: RE: Updated DSMC slides

Thanks Michele

By the way what did Hercules die of??

On another note, we had previously in the version sent to the DSMC for the December planned conference call indicated that we were going to lower the hi alarm limit to 94%. We have now removed that. Do any of you believe that the DSMC will express concern about this? I would indicate that this decision was based on the results of the analyses and further discussion with the Steering Committee, and the actual SpO2 durations > 96%.

I would appreciate knowing if any of you have a concern about this.

Be well

Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@case.edu]
Sent: Monday, January 16, 2006 1:47 PM
To: Higgins, Rose; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
Subject: Updated DSMC slides

Neil:

Thanks again for all of your efforts. I went through your revised slides with my editor hat on: I have edited the style and format to make all similar. None of the content is changed: just the style of presentation in general to make it more simple and to use sub-bullets to help the data standout from the text.

Hope you find this helpful.

Michele

That which does not kill you, will make you stronger.

By the end of this,you should be Herculean in strength!

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 13, 2006

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."**

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving Oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became significantly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by > 9% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- **The optimal saturation range for ELBW is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Evidence for Currently used SpO2 Ranges is Lacking

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.**

Published Evidence

- **Sun et al compared units with upper limits of >95% with those of ≤ 95%**
  - (Ped Res 2002, 51:350A)
- **Tin et al reported units by the limits they set without any individual patient data.**
  - Arch Dis Child 2001;84:f106)

Published Evidence

- **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 practice changes including lowering the SpO2 limit – Did not provide actual data**

  -Chow et al, Pediatr 2003;111:339

- ***All of these observational studies suggested that lower SpO2 limits were associated with less ROP.***

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting this data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- **14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks**
- **Study performed to document practice prior to a trial with design parallel to SUPPORT**
- **Reported SpO2 limits ranged:**
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- **Median SpO2 in Hagadorn = 95%**
- **Median SpO2 from SUPPORT –**
  - All infants in trial = 92% and 94%
  - Infants in Oxygen = 91% and 93%
- **Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.**

Additional Evidence

- **Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%**
- **Hagadorn study-**
  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants-**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW nonSUPPORT**
  51% time SpO2 > 95%

84% and 96%: switch from altered to all real values

- These points are where altered and real values overlap, by nature of the SUPPORT SpO2 algorithm
- Entirely real SpO2 values in SUPPORT are > 96% and < 84%
- Therefore, subsequent data will be presented for values > 96% and < 84%, rather than the expected >95% and <85%

SpO2 values of SUPPORT infants in Room Air

- **Infants in room air had a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.**

	91%- 95% Group	85% - 89% Group
Room Air	**52.7%**	**46.1%**
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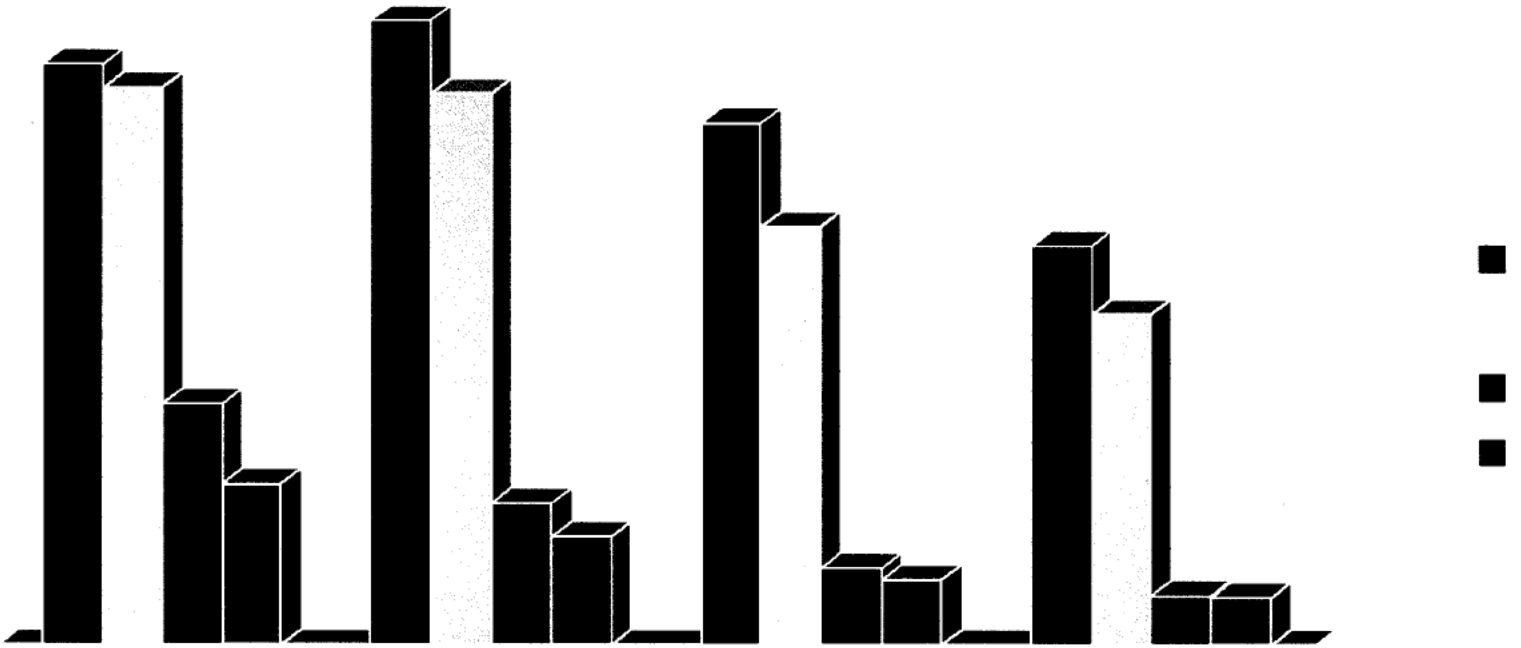
Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



5-04884

Impact of the Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **This data can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Impact of Algorithm

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Impact of Algorithm

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%
- Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.
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DSMC pt 2: Futility regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
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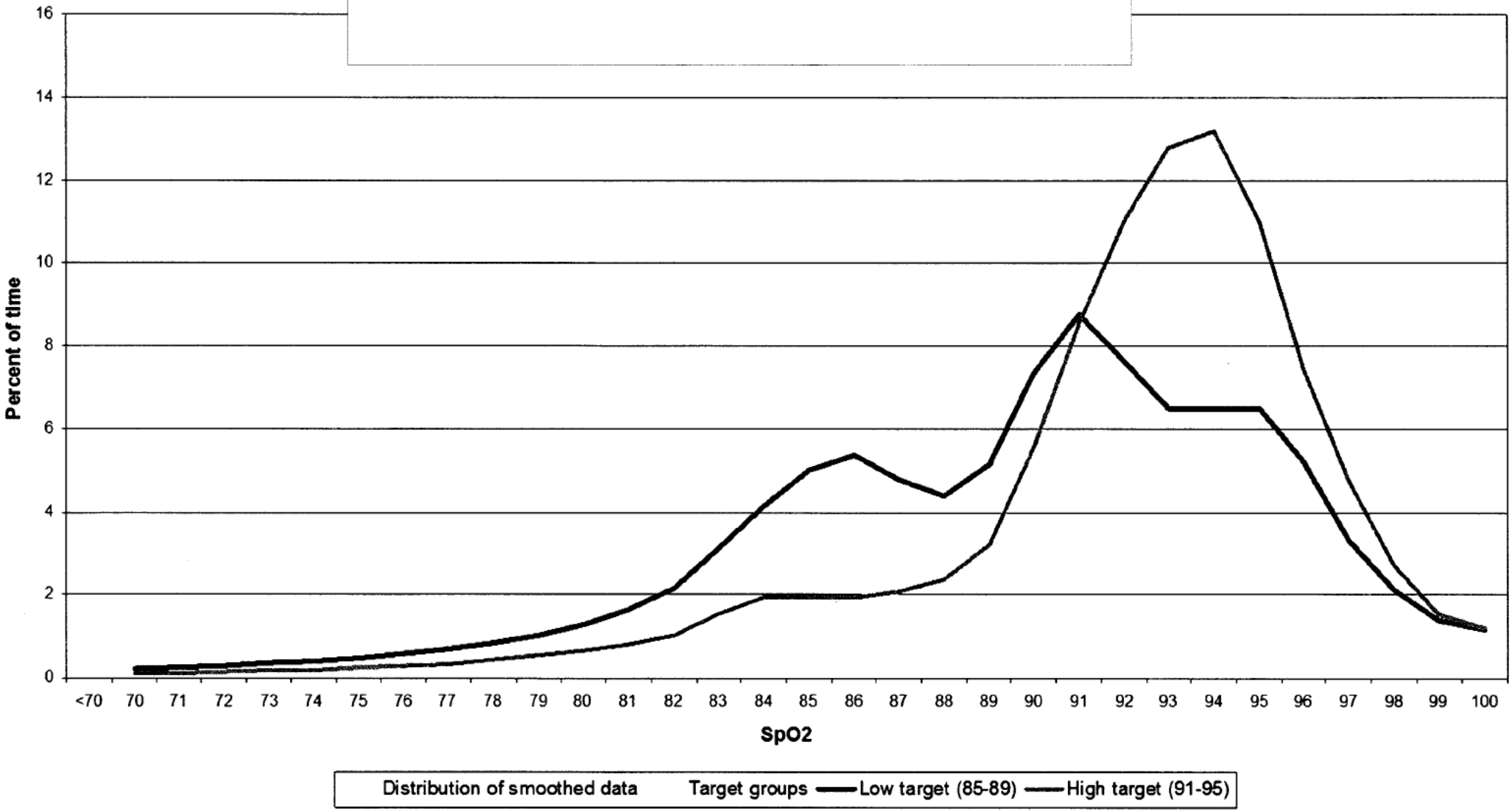

Slide 26

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Pediatrics, 12/16/2005

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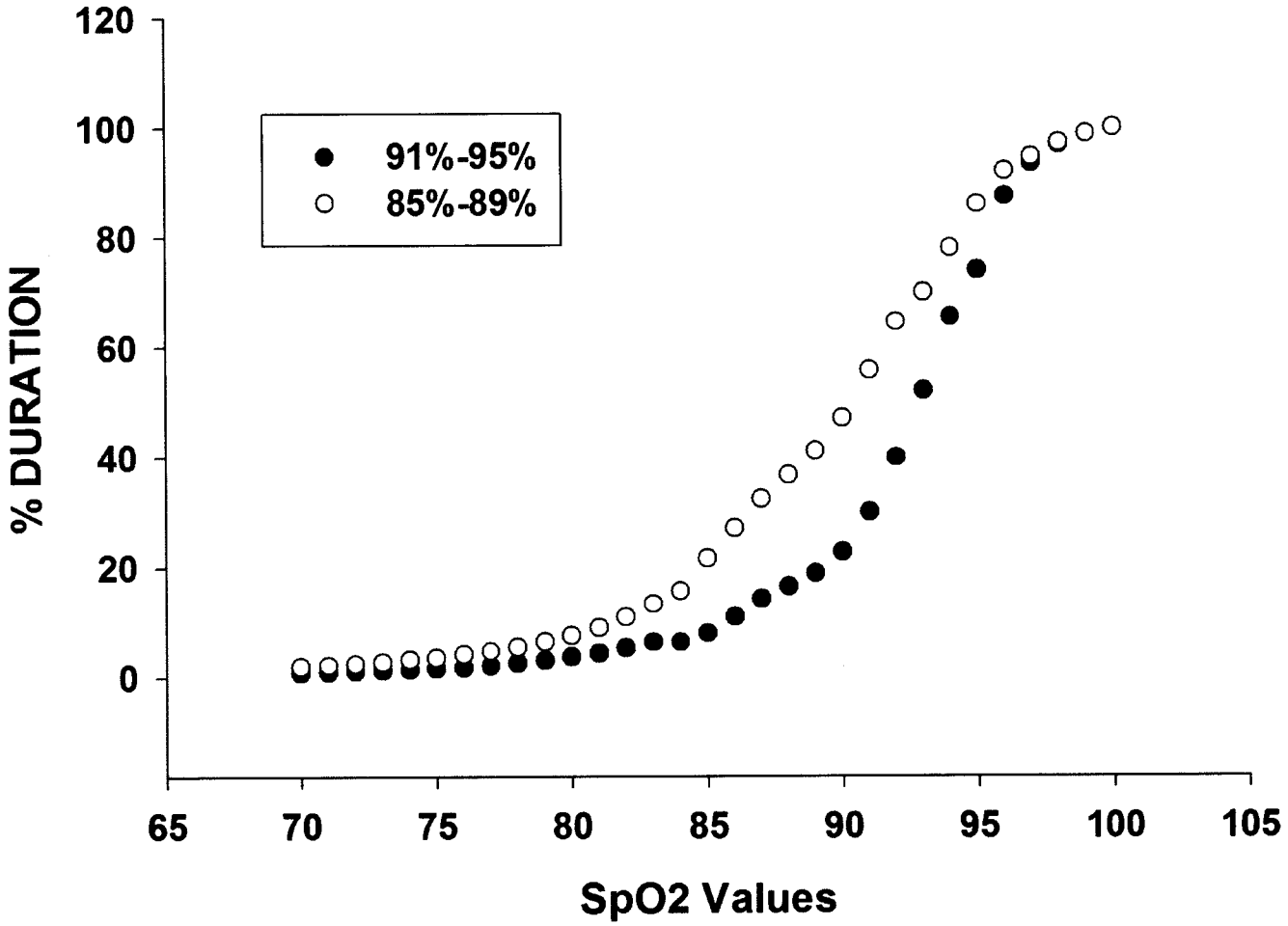

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From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	FW: SUPPORT - DSMC Response
Date:	Tuesday, January 17, 2006 11:24:19 PM
Attachments:	DSMC Jan 17 revised.ppt

Hi Rose
Let me know if you can open this
Neil

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, January 17, 2006 5:07 PM
To: 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; Das, Abhik; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
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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

Jan 24, 2006

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  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants-**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW non-SUPPORT 51% time SpO2 > 95%**

Effects of Room Air on SpO2 > 95%

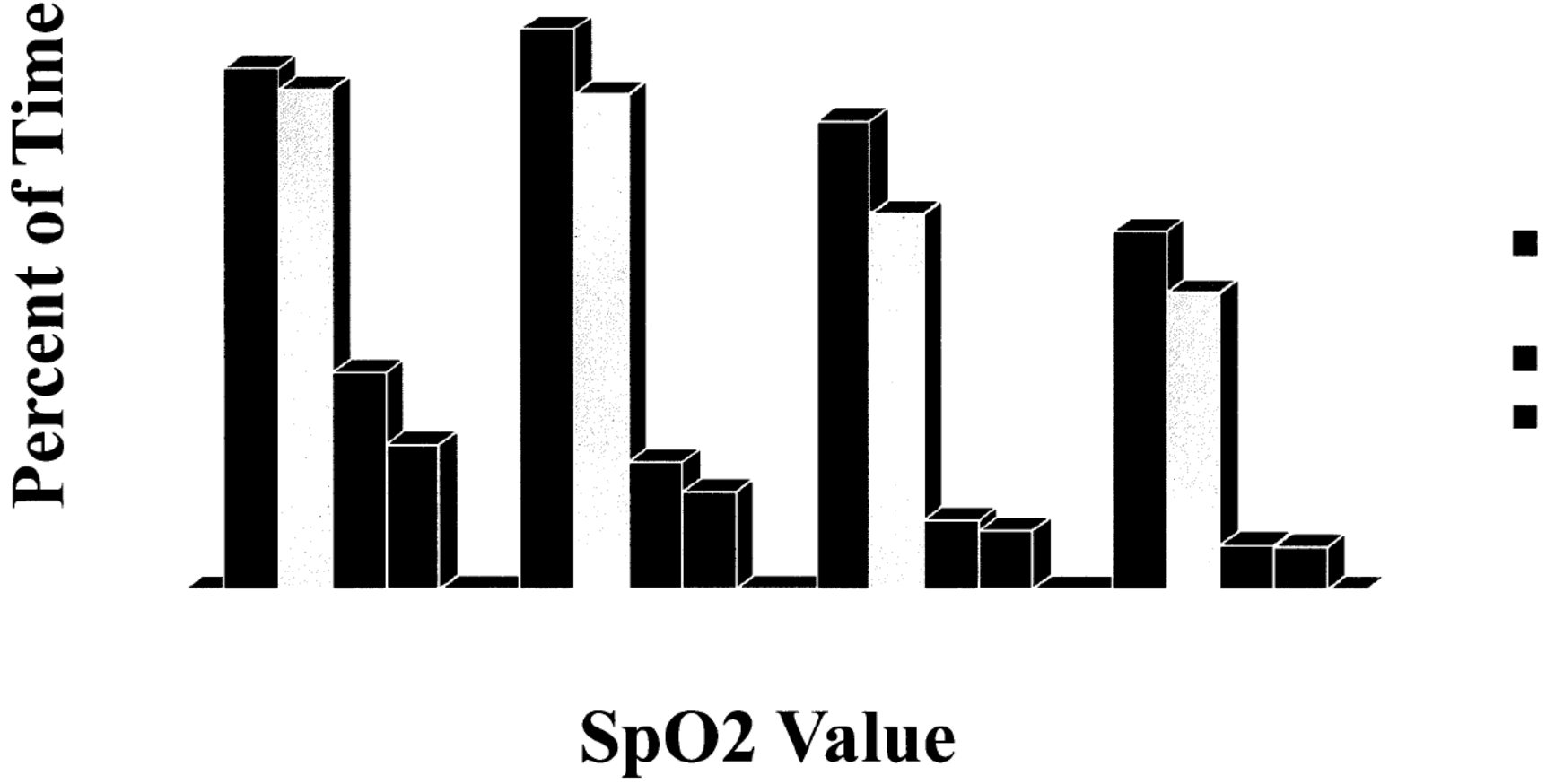
- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time
- The Median SpO2 values while in Room air for the 91%-95% and 85%-89% Groups are 97% and 96%
- Median SpO2 in healthy preterm infants in room air = 97% (Ng et al Arch Dis Child 1998;79:F64)
- Infants in room air can not have changes made to their inspired oxygen to lower their SpO2s.

SpO2 values of SUPPORT infants in Room Air

- **Infants in room air had a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.**

	91%- 95% Group	85% - 89% Group
Room Air	**52.7%**	**46.1%**
Oxygen	**12.6%**	**9.4%**

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



The Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **These files can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Evaluation of SpO2 Information

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Evaluation of SpO2 ranges

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- **Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%**
- **Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.**
- **This incorrectly assigned some infants in RA to the Oxygen analysis.**

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to greater durations of SpO2 > 95% while receiving oxygen than ELBW infants currently receiving usual care.**
- **Previous analyses overstated the exposure.**
- **Most of the overestimate was from misclassification of infants in partial oxygen.**

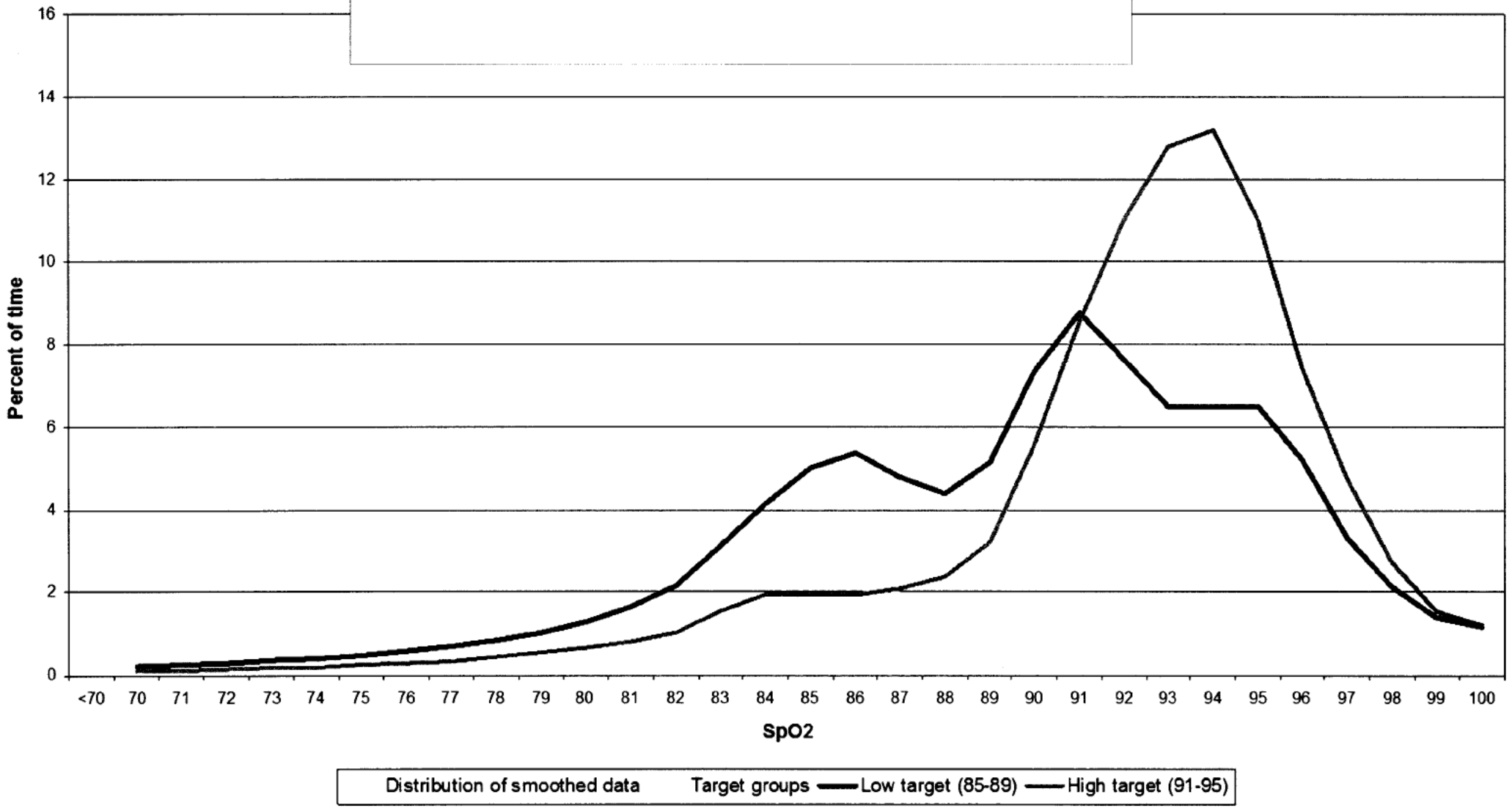
Safety Issue of SpO2 > 95%

- **This trial will help to determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**

Futility Regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - **Mean all infants – 90% vs 92%**
  - **Median all infants – 92% vs 94%**
  - **Median infants in oxygen at all 3 data points - 91% vs 93%**
- **Time with an SpO2 of ≤90% shows a difference of > 24%**
  - **91% - 95% Group = 22.8%**
  - **85% - 89% Group = 47.6%**

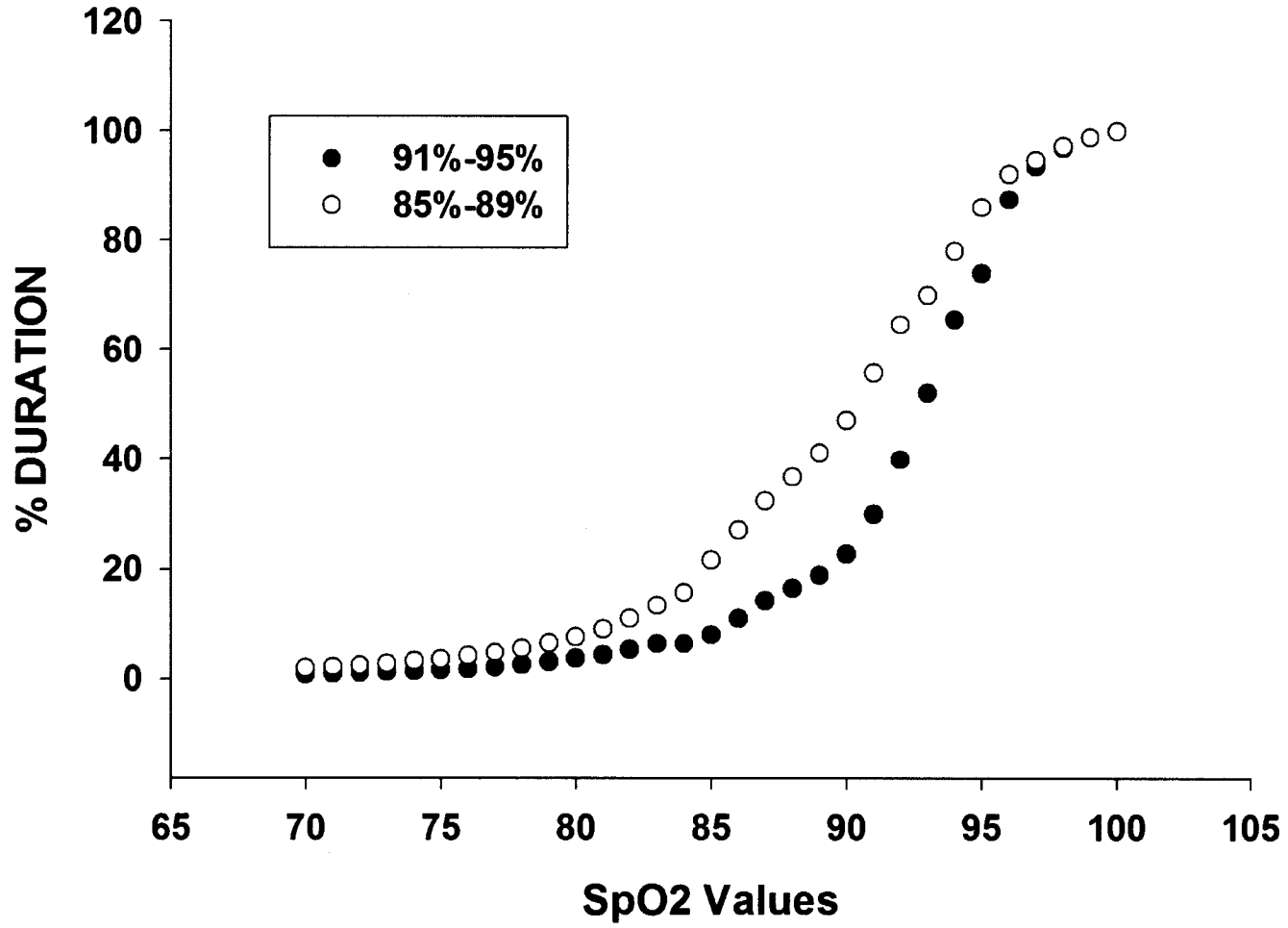
Based on Oxygen Days



Slide 24

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



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**

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - **91%-95% group = 26.6%**
  - **85%-89% group = 35.5%**
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

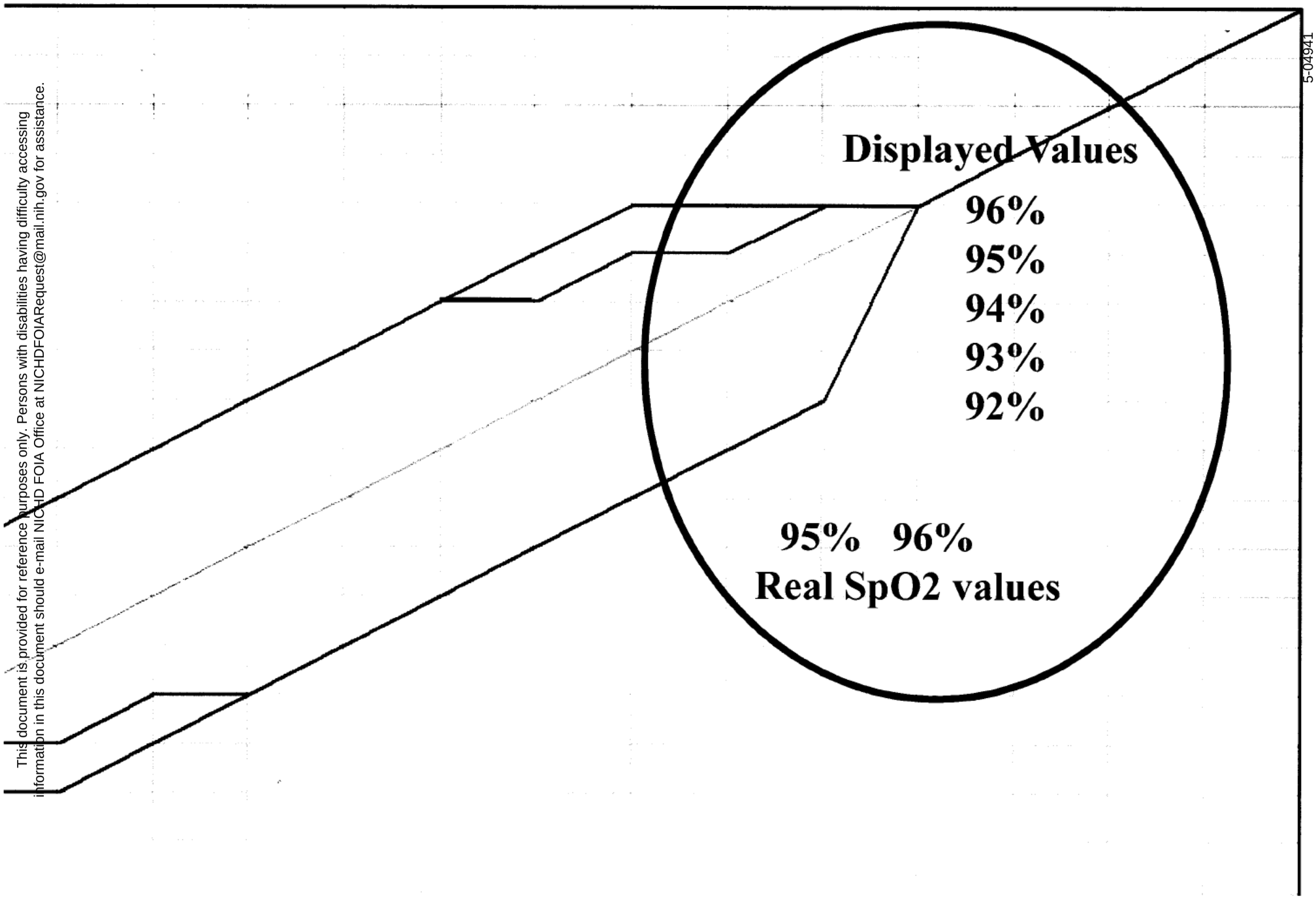
7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Conclusion

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

SpO2 Algorithm

- **These SpO2 values represent an overlap of altered and real values of the SUPPORT SpO2 algorithm**
- **All displayed SpO2 values in SUPPORT > 96% and < 84% represent the actual unaltered SpO2**
- **Therefore, subsequent data will be presented for values > 96% and < 84%, rather than the expected >95% and <85%**



From:	Neil Finer
To:	"Edward Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Shahnaz Duara"; "Wally Carlo"; "M.D." "Avroy A. Fanaroff"; "Michele"; "Abhik Das"; "Betty Hastings"; "Ken Poole"; "Maynard Rasmussen"; Wade Rich
Subject:	RE:
Date:	Tuesday, January 17, 2006 8:06:00 PM

Hi Ed
Thanks for your comments – they are a great help
I have answered them below

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Tuesday, January 17, 2006 10:24 AM
To: higginsr@mail.nih.gov; 'Shahnaz Duara'; 'Wally Carlo'; M.D.' 'Avroy A. Fanaroff; 'Michele'; Abhik Das; 'Betty Hastings'; 'Ken Poole'; 'Maynard Rasmussen'; Neil Finer; 'Wade Rich'
Subject: Re:

Neil - suggestions:

change date on slide 1 to date of meeting. Done

slide 5, second bullet: "The proportion of time in RA was 9% greater in the low target group compared to the high target group." I see the point, but I would expect this to produce a greater proportion of time with high sats in the low target group. The logic we present is that RA leads to high sats; low target spent more time in RA; but high target had more time with high sats. Will this make sense to DSMC? This is a very good point. I believe that the reason for this finding is that the 85-89 infants were placed in RA because of the oximeters reading 90-94% when the actual SpO2s were lower as intended. Thus, they would not initially have a higher duration of hi SpO2s. As they fully recovered they would experience higher SpO2s but probably after the study oximeter was off.

slide 6: word "appropriate" could be deleted. "durations are" Done I think

this could be a question from DSMC: We have deleted from consideration days in which the infant was sometimes receiving supplemental oxygen and sometimes receiving RA. Theoretically, these could be the days of highest SpO2 because infants were well enough to receive RA (known to be associated with high sats), yet for part of the day received suppl. O2 potentially leading to even higher sats. To respond to this question, we should know how many days were excluded from the analysis by excluding days of part suppl. O2 and part RA. The times when infants are in oxygen they actually have lower durations of high SpO2s, at least from our data. As noted above the 85-89 group would also have lower actual SpO2 when initially in RA

slide 25 - rather than say "excessive duration >95%", how about saying "no more time, and possibly less time, with SpO2 > 95% than usual care the best it can be estimated today" Done - see if reads OK

do you think we should collect better data to estimate actual differences in area under the fiO2 curve? I am reluctant to look at more data.

Hope this helps.
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 513-636-0180
Fax 513-636-0171
www.cincinnatichildrens.org/cprc

>>> "Neil Finer" <nfiner@ucsd.edu> 01/14/2006 8:13:12 PM >>>
Hi Everyone
I have tried to incorporate all the ideas from the meeting. There are more slides because I made them less crowded. They will not take longer to present. I also added an explanation (slide 14 I think) about room air so that the non MDS would understand why room air is an issue.
I would appreciate your thoughts.
I think this presentation can be done in about 20 minutes and we can use the discussion time to further explain any issues.
I have removed all the titles which indicated DSMC response.
I feel that we are in good shape to justify the continuation of SUPPORT.
Regards
Neil Finer

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"
Subject:	FW: SUPPORT updates
Date:	Tuesday, January 17, 2006 7:53:22 PM
Attachments:	Percent of time spent at each SpO2 value (supp O2) 1-17-06.doc Percent of time spent at each SpO2 value (FiO2 gt21 all time points) 1-17-06.doc Percent of time spent at each SpO2 value (room air) 1-17-06.doc

FYI
I have not changed the slide values as the results are almost all identical.
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, January 17, 2006 2:28 PM
To: Neil Finer; Wade Rich
Cc: Das, Abhik; Poole, W. Kenneth
Subject: SUPPORT updates

Attached are updates of the "Percent of time spent at each SpO2 value" documents I created for you at the beginning of December. The results are virtually identical to the last run. At that time, we had oximeter data on 166 infants; we now have data on 182. Tomorrow, I intend to send you an update of the daily FiO2 data I sent back on 12/5.

To answer your question about median SpO2 for infants on room air, the medians are 97 for the High target (91-95) group and (most likely) 96 for the Low target (85-89) group. Since SpO2 values of 93-96 are lumped together for the Low target group, we only know for certain that the median is between 93 and 96. However, unless the infants spent <5% of their time at SpO2=96 (which seems very unlikely given the data) the median SpO2 for the group is 96. The graphs attached might make that clearer.

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: Saturday, January 14, 2006 7:49 PM
To: Gantz, Marie; Das, Abhik
Cc: 'Avroy A. Fanaroff, M.D.'; Hastings, Betty J.; 'Ed Donovan'; higginsr@mail.nih.gov; Poole, W. Kenneth; 'Maynard Rasmussen'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'; 'Wally Carlo'
Subject:

Hi Marie and Abhik
Can you calculate the median SpO2 for the infants while in room air by group. We know from previous studies that this value is around 97%. It looks to me be about 94% for the 85-89 group and 97 for the 91-95 group.
Many thanks
Neil

Percent of time spent at each SpO2 value
Days on which any supplemental oxygen was given
(For day of life 1-14, at least one FiO2 measurement >0.21 on SUPP05, or for day of life 15+, Oxygen=Yes on SUPP11)
Data processed as of 1/17/2006

Data included in tables and graphs

Infants included	High target (91-95)	Low target (85-89)	Total
Number	86	96	182
Hours	65665	61130	126795

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	1.13	1.13	2.04	2.04
70	0.14	1.27	0.25	2.29
71	0.16	1.43	0.29	2.59
72	0.19	1.62	0.34	2.92
73	0.22	1.84	0.39	3.31
74	0.25	2.09	0.45	3.76
75	0.30	2.39	0.52	4.28
76	0.35	2.74	0.61	4.88
77	0.42	3.16	0.71	5.59
78	0.50	3.65	0.84	6.43
79	0.60	4.25	1.01	7.44
80	0.71	4.96	1.20	8.65
81	0.86	5.82	1.45	10.09
82	1.04	6.86	1.76	11.86
83	1.26	8.12	2.15	14.01
84	0.00	8.12	1.81	15.82
84.25	0.00	8.12	0.74	16.56
84.5	0.00	8.12	0.79	17.34
84.75	0.00	8.12	0.84	18.18
85	0.00	8.12	2.05	20.23
85.5	7.40	15.52	0.00	20.23
86	0.00	15.52	3.83	24.06
87	0.00	15.52	3.61	27.67
88	2.19	17.71	3.24	30.91
89	2.45	20.16	3.39	34.30
90	3.39	23.55	4.48	38.78
91	5.46	29.01	6.61	45.39
92	7.28	36.28	7.47	52.86
93	8.93	45.21	0.00	52.86
94	10.31	55.52	0.00	52.86
94.5	0.00	55.52	30.49	83.35
95	7.34	62.86	0.00	83.35
95.25	2.97	65.83	0.00	83.35
95.5	2.88	68.71	0.00	83.35
95.75	2.85	71.56	0.00	83.35
96	6.66	78.21	0.00	83.35
97	8.56	86.77	6.29	89.63
98	6.32	93.09	4.77	94.40
99	3.94	97.03	3.08	97.49
100	2.97	100.00	2.51	100.00

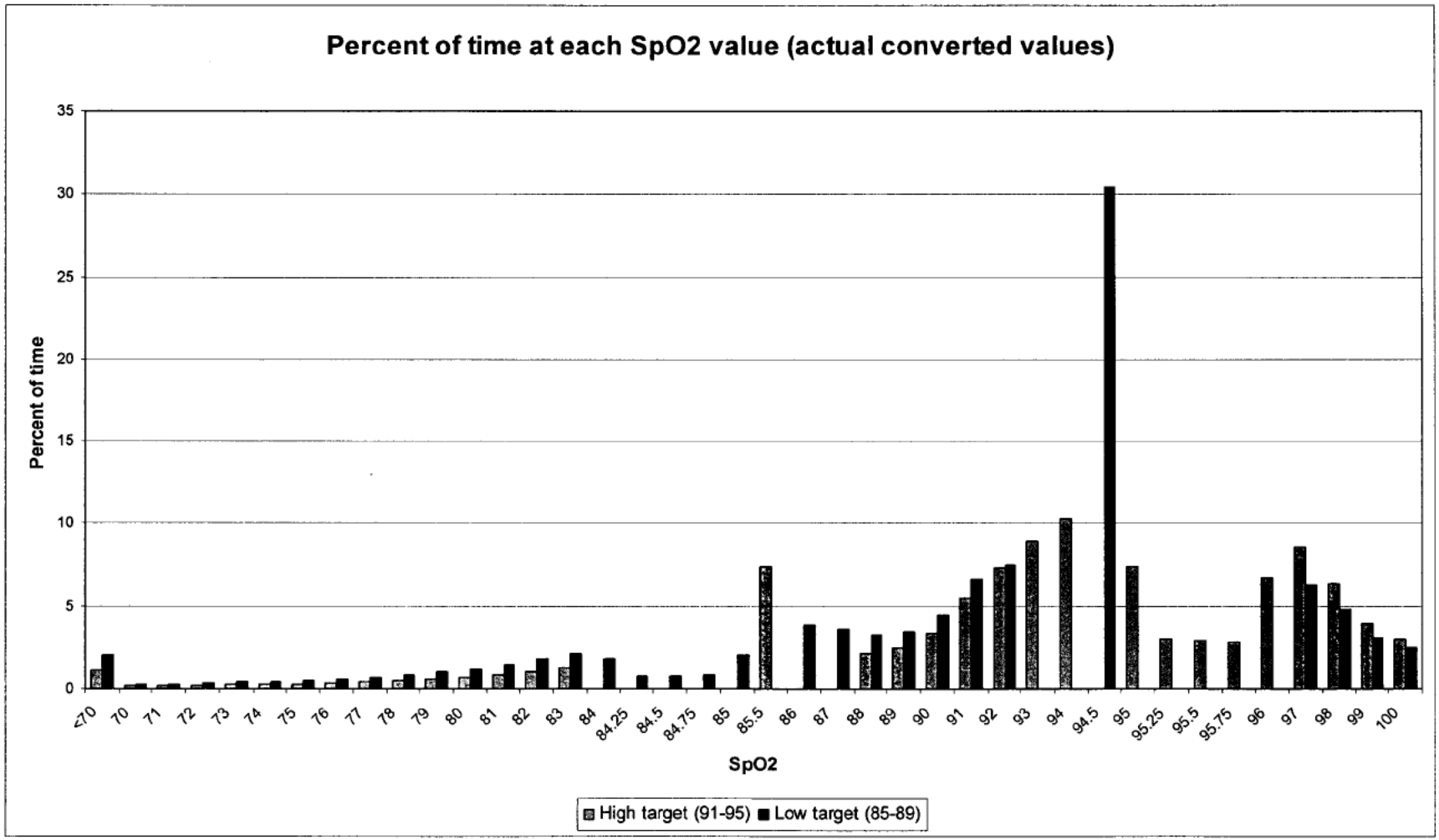
Median SpO2

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

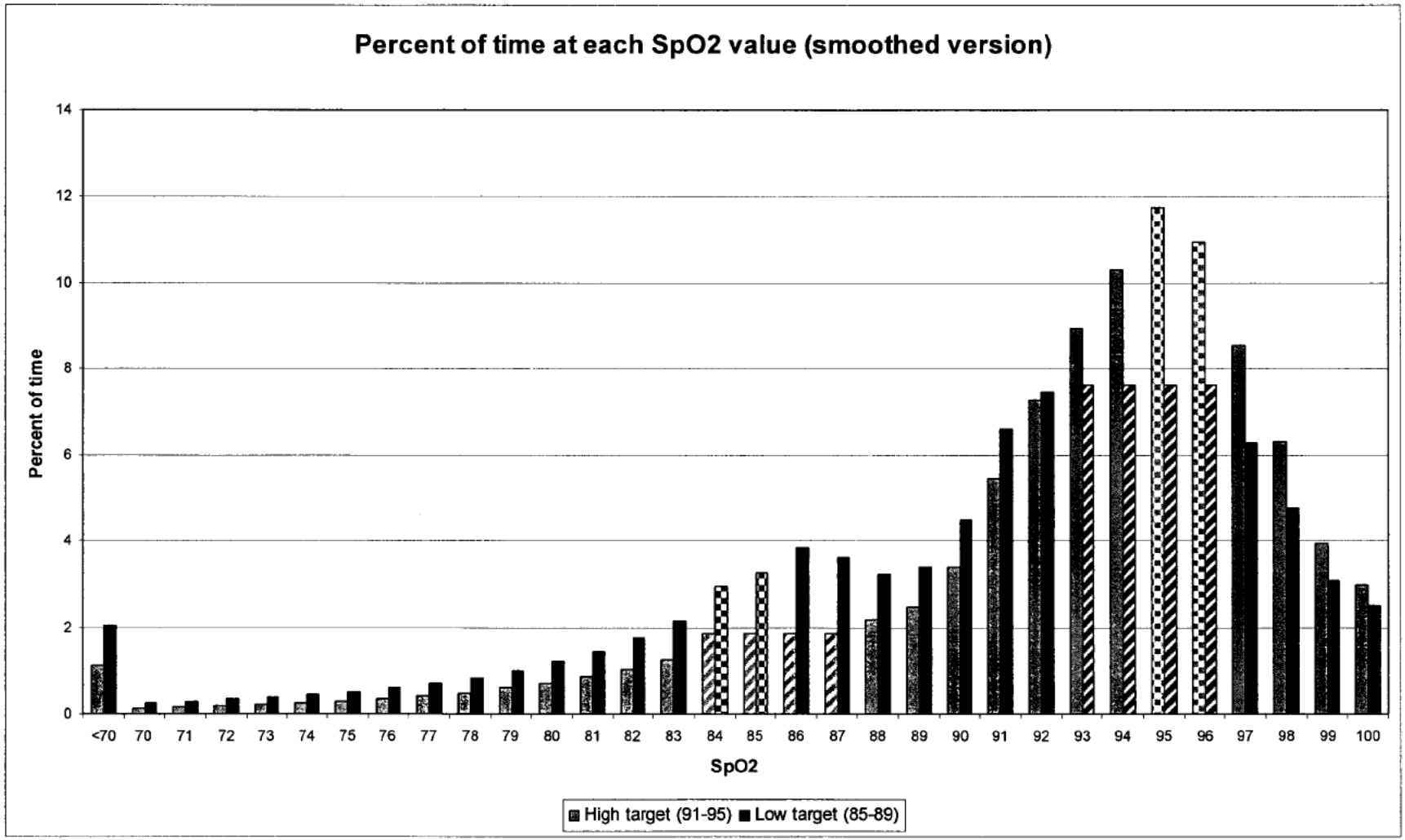
Percent of time of spent at SpO2 <84 and >96

Range	High target (91-95)	Low target (85-89)
<84	8.12	14.01
>96	21.79	16.65

The graph below displays each individual converted SpO2 value



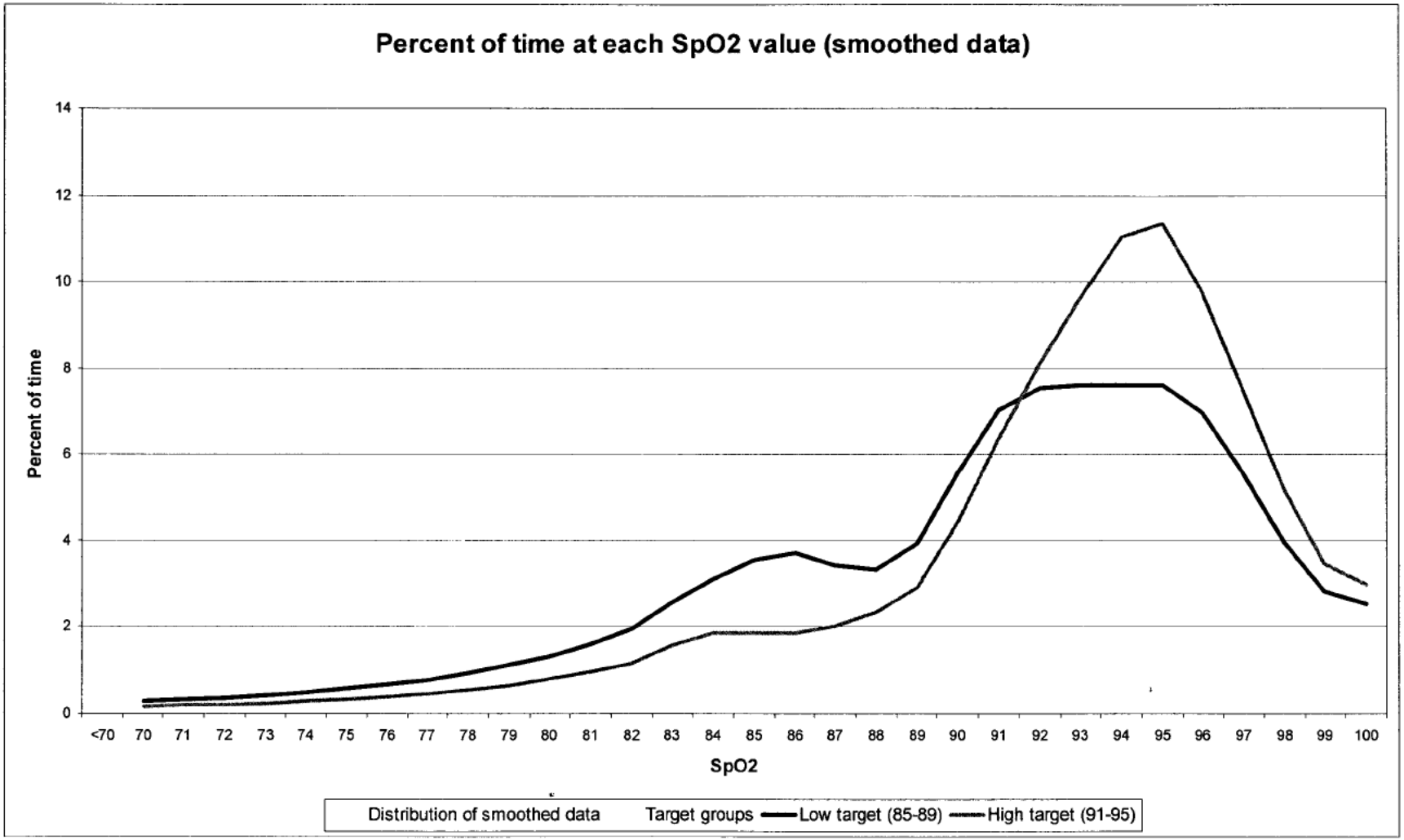
In the graph below, the converted SpO2 values have been smoothed to give a better idea of the distribution. Adjustments made to smooth the data are listed on the following page. Patterns are used to identify altered values.



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



Percent of time spent at each SpO2 value
Days on which FiO2 was >0.21 at all time points recorded (days of life 1-14 only)
(FiO2 was recorded on form SUPP05 at three time points each day, for days of life 1-14. On day of life1, fewer than three time points may have been recorded.)
Data processed as of 1/17/2006

Data included in tables and graphs

Infants included	High target (91-95)	Low target (85-89)	Total
Number	76	72	148
Hours	10898	9409	20307

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	0.76	0.76	1.74	1.74
70	0.09	0.85	0.21	1.95
71	0.11	0.96	0.24	2.19
72	0.12	1.08	0.28	2.47
73	0.15	1.22	0.33	2.80
74	0.17	1.39	0.38	3.18
75	0.21	1.60	0.45	3.63
76	0.25	1.85	0.54	4.17
77	0.30	2.15	0.63	4.80
78	0.36	2.51	0.77	5.57
79	0.46	2.97	0.95	6.52
80	0.57	3.54	1.17	7.68
81	0.69	4.23	1.49	9.17
82	0.85	5.08	1.91	11.08
83	1.07	6.15	2.47	13.54
84	0.00	6.15	2.28	15.82
84.25	0.00	6.15	0.96	16.78
84.5	0.00	6.15	1.03	17.81
84.75	0.00	6.15	1.14	18.95
85	0.00	6.15	2.83	21.78
85.5	7.25	13.39	0.00	21.78
86	0.00	13.39	5.54	27.31
87	0.00	13.39	5.20	32.51
88	2.25	15.64	4.33	36.84
89	2.44	18.09	4.34	41.18
90	3.73	21.82	5.95	47.13
91	6.91	28.72	8.74	55.87
92	9.53	38.25	8.82	64.69
93	11.74	49.99	0.00	64.69
94	13.12	63.12	0.00	64.69
94.5	0.00	63.12	25.89	90.58
95	8.77	71.89	0.00	90.58
95.25	3.34	75.23	0.00	90.58
95.5	2.76	77.99	0.00	90.58
95.75	2.56	80.55	0.00	90.58
96	5.40	85.95	0.00	90.58
97	6.52	92.47	3.95	94.53
98	3.94	96.41	2.71	97.24
99	2.20	98.61	1.60	98.84
100	1.39	100.00	1.16	100.00

Median SpO2

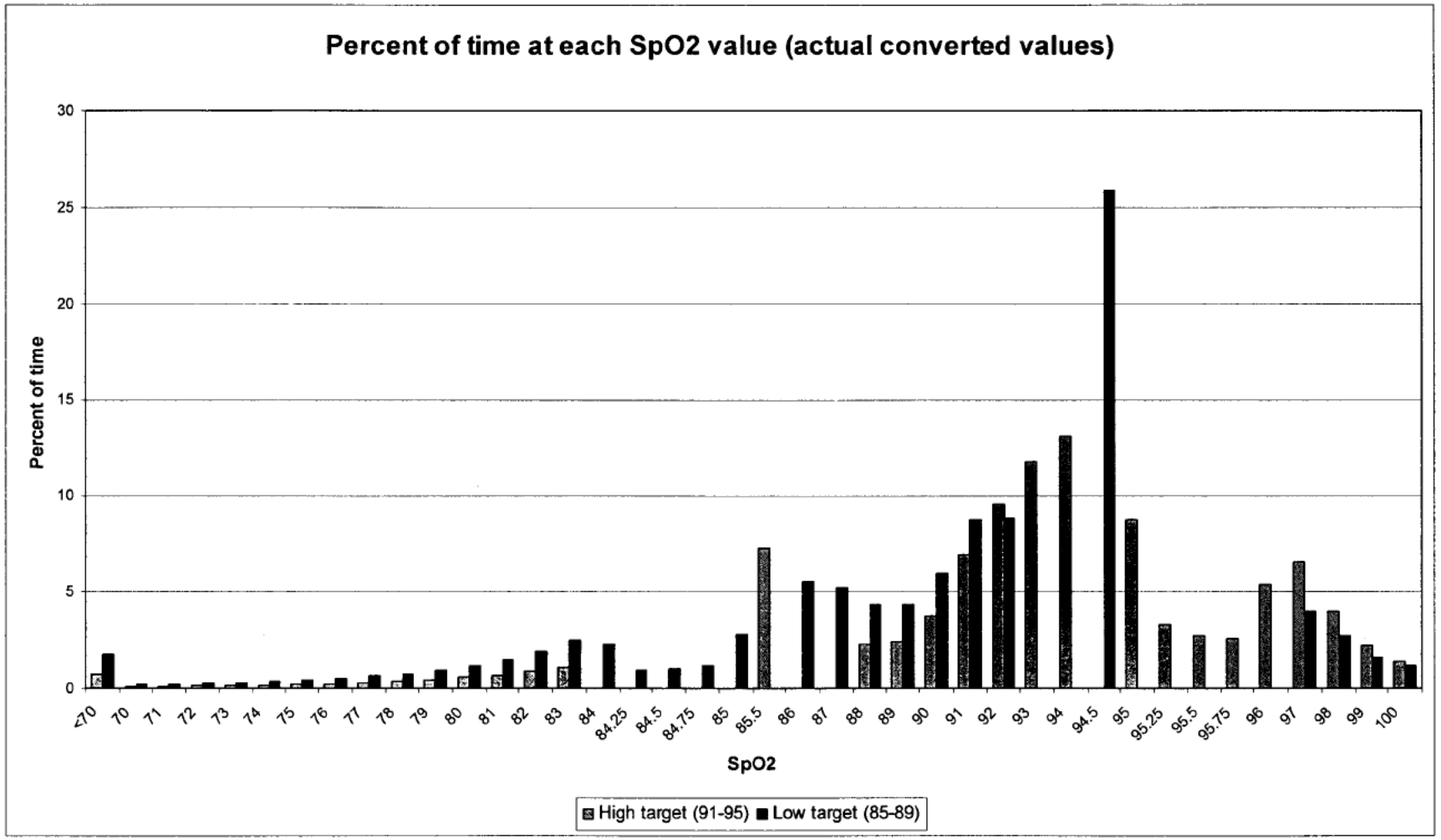
Note: For the High target group, the percent of time spent at SpO2<=93 was 49.99%, so the median occurred almost exactly between 93 and 94.

	High target (91-95)	Low target (85-89)
Median	93.5	91

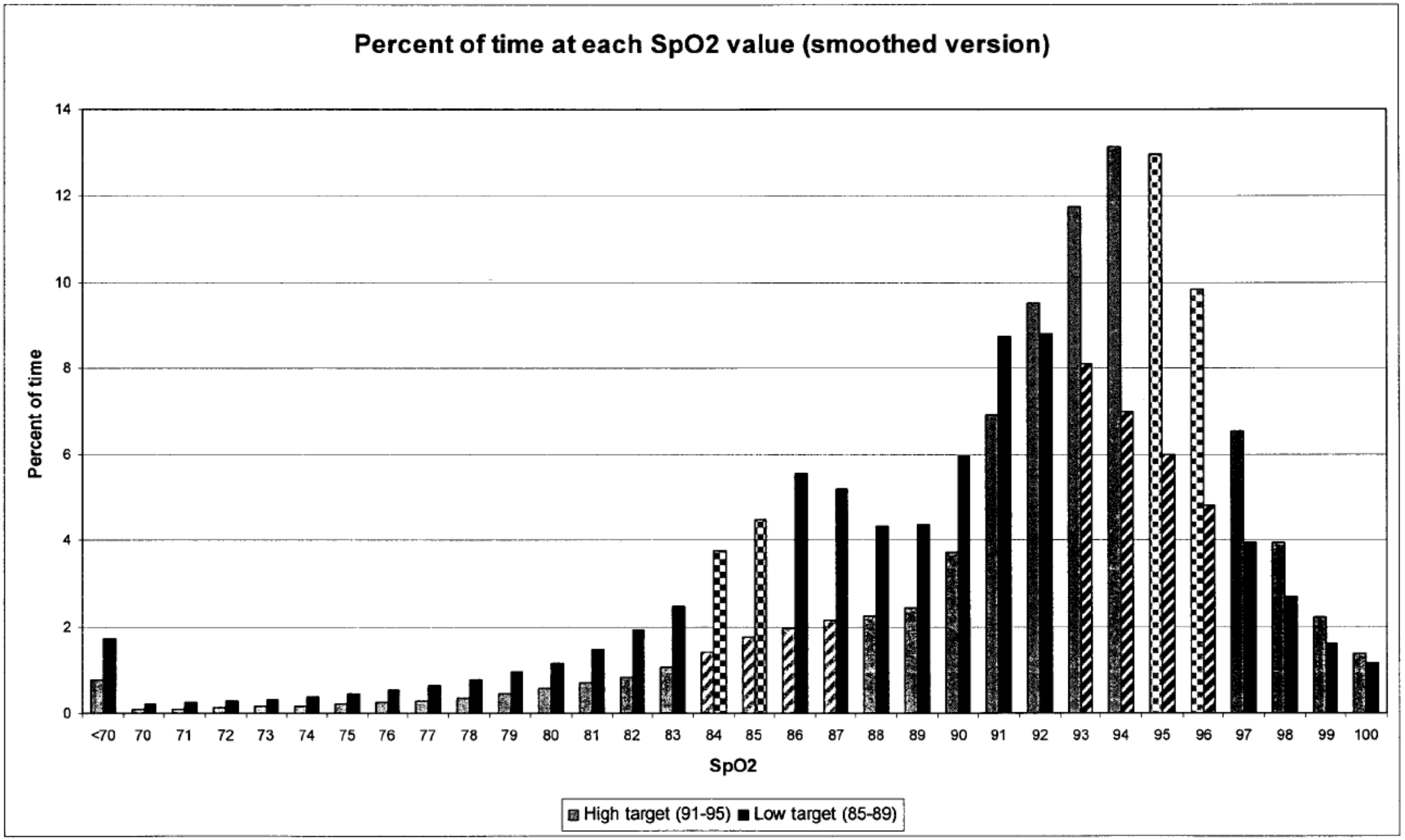
Percent of time of spent at SpO2 <84 and >96

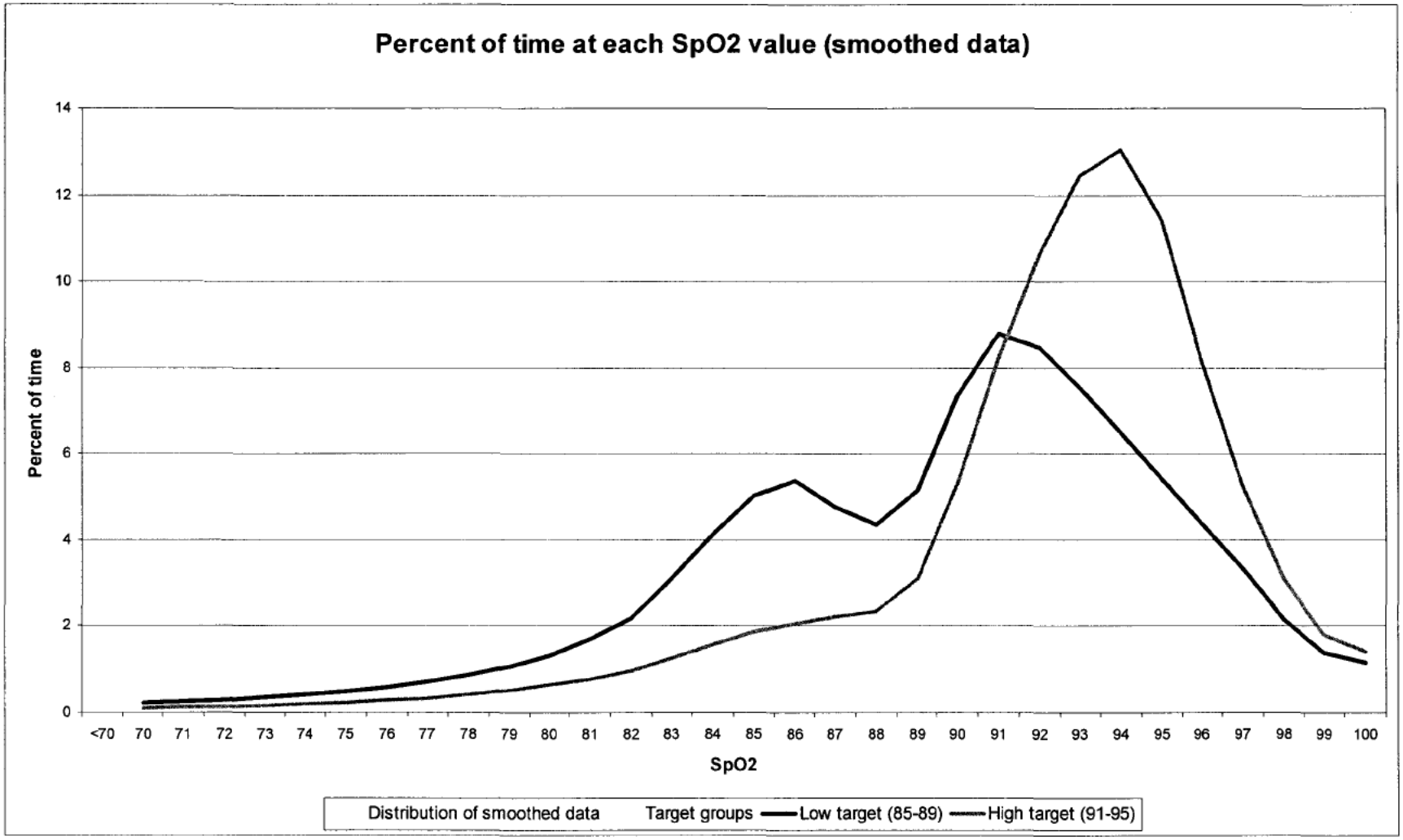
Range	High target (91-95)	Low target (85-89)
<84	6.15	13.54
>96	14.05	9.42

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.





Percent of time spent at each SpO2 value
Days on room air only
(For day of life 1-14, all values of FiO2 recorded on SUPP05 were 0.21, or for day of life 15+, Oxygen=No or Highest level of support=7 (no support) on SUPP11)
Data processed as of 1/17/2006

Data included in tables and graphs

Infants included	High target (91-95)	Low target (85-89)	Total
Number	59	73	132
Hours	15125	17764	32889

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	0.45	0.45	0.40	0.40
70	0.05	0.50	0.05	0.45
71	0.06	0.57	0.06	0.52
72	0.07	0.64	0.07	0.59
73	0.08	0.72	0.08	0.67
74	0.10	0.82	0.10	0.77
75	0.11	0.93	0.12	0.89
76	0.13	1.06	0.14	1.04
77	0.15	1.21	0.17	1.21
78	0.18	1.38	0.21	1.42
79	0.21	1.59	0.26	1.68
80	0.25	1.84	0.31	1.99
81	0.30	2.14	0.39	2.38
82	0.36	2.50	0.48	2.85
83	0.43	2.93	0.61	3.46
84	0.00	2.93	0.49	3.95
84.25	0.00	2.93	0.20	4.15
84.5	0.00	2.93	0.22	4.37
84.75	0.00	2.93	0.23	4.61
85	0.00	2.93	0.60	5.20
85.5	2.66	5.60	0.00	5.20
86	0.00	5.60	1.19	6.39
87	0.00	5.60	1.24	7.63
88	0.97	6.57	1.27	8.90
89	1.17	7.74	1.49	10.39
90	1.56	9.30	2.11	12.51
91	2.36	11.66	3.35	15.85
92	3.47	15.13	4.58	20.43
93	4.89	20.02	0.00	20.43
94	6.86	26.89	0.00	20.43
94.5	0.00	26.89	34.46	54.89
95	5.89	32.77	0.00	54.89
95.25	2.59	35.36	0.00	54.89
95.5	2.69	38.05	0.00	54.89
95.75	2.86	40.91	0.00	54.89
96	7.36	48.27	0.00	54.89
97	14.18	62.45	13.57	68.46
98	15.09	77.54	13.33	81.79
99	12.53	90.07	10.13	91.92

100	9.93	100.00	8.08	100.00

Median SpO2

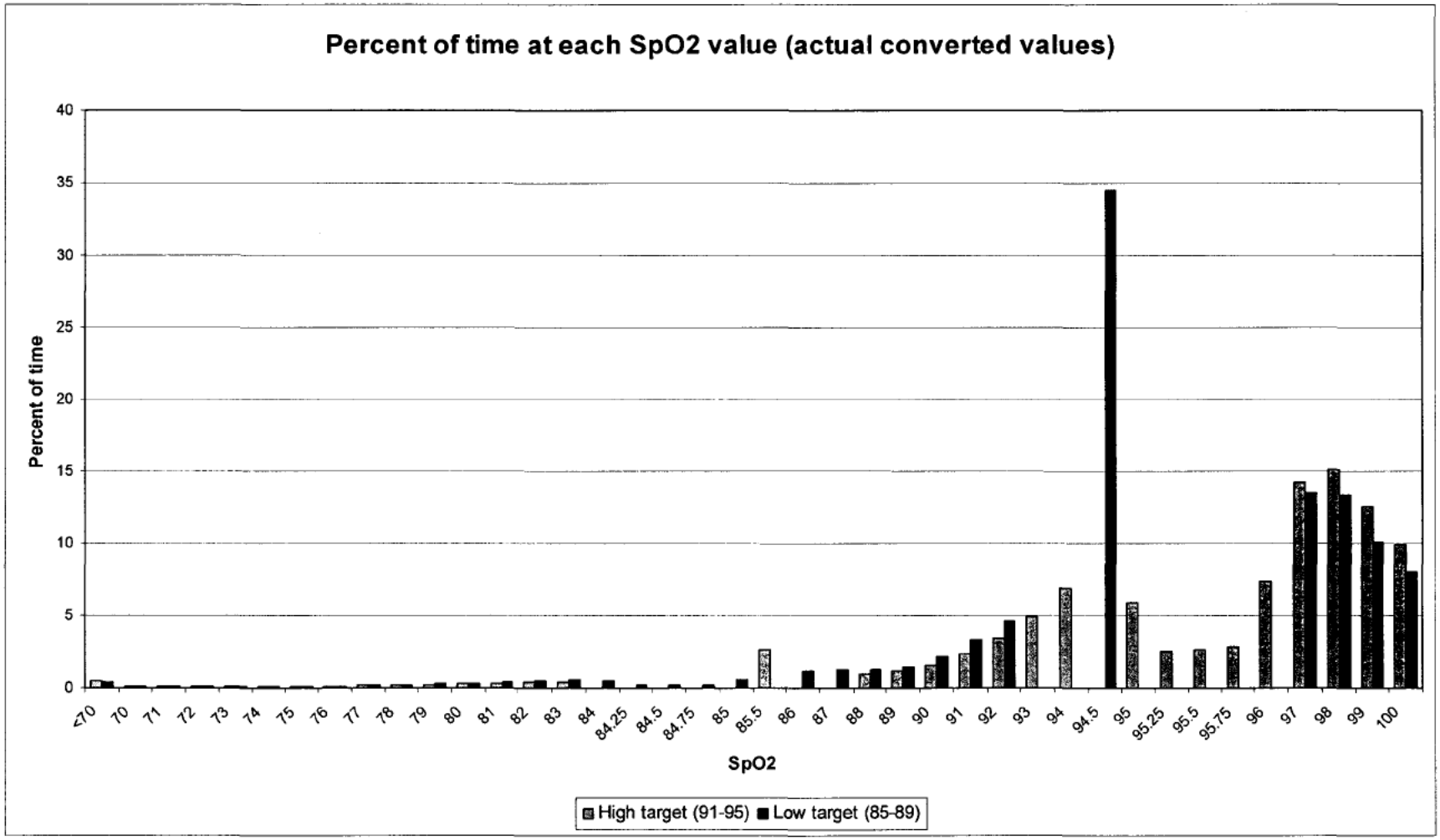
Note: Since SpO2 values of 93 to 96 are lumped together for the Low target group, we only know for certain that the median is somewhere in the range 93-96. Based on the smoothed graphs, below, however, it looks most likely that the median for the low target group is 96.

	High target (91-95)	Low target (85-89)
Median	97	93-96

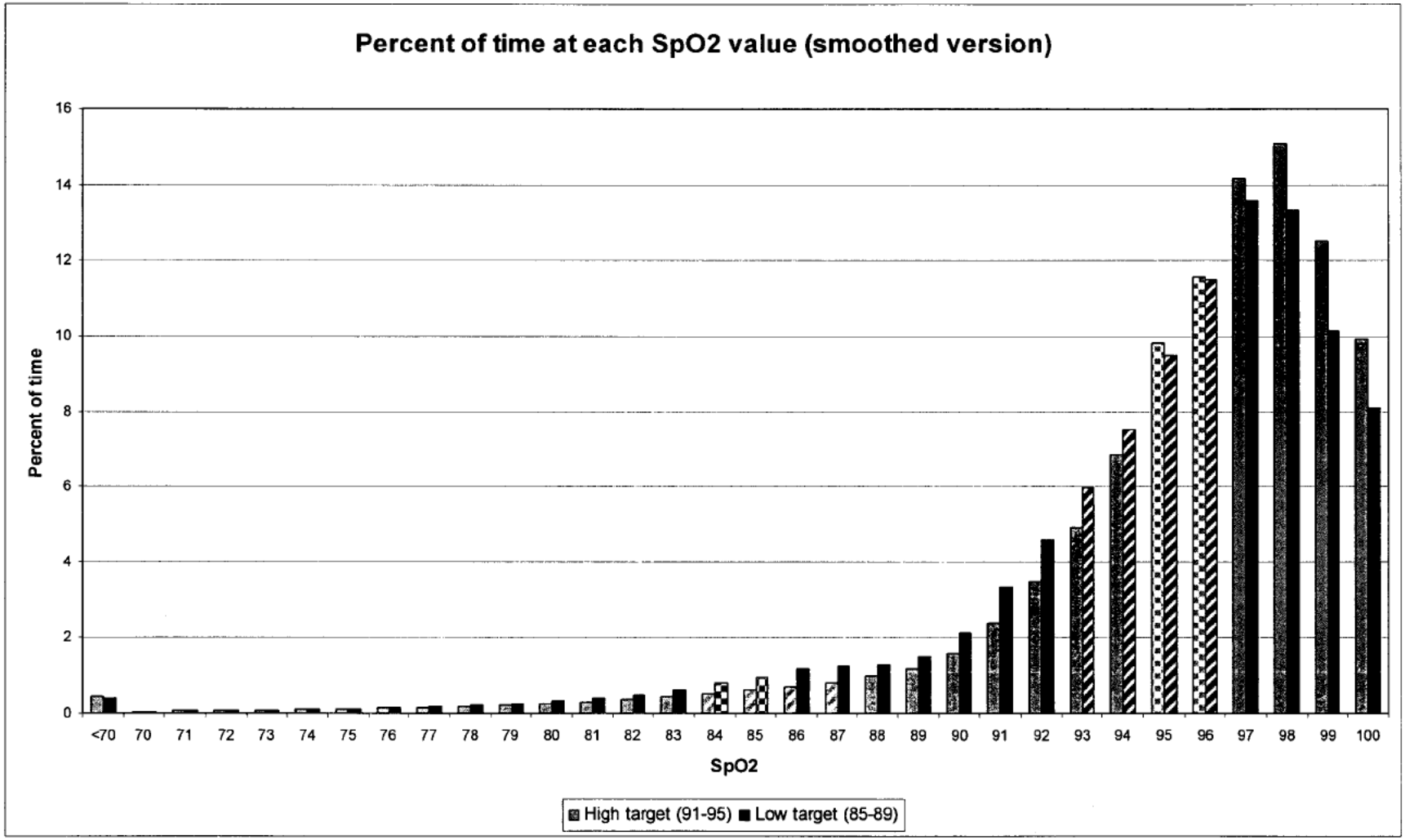
Percent of time of spent at SpO2 <84 and >96

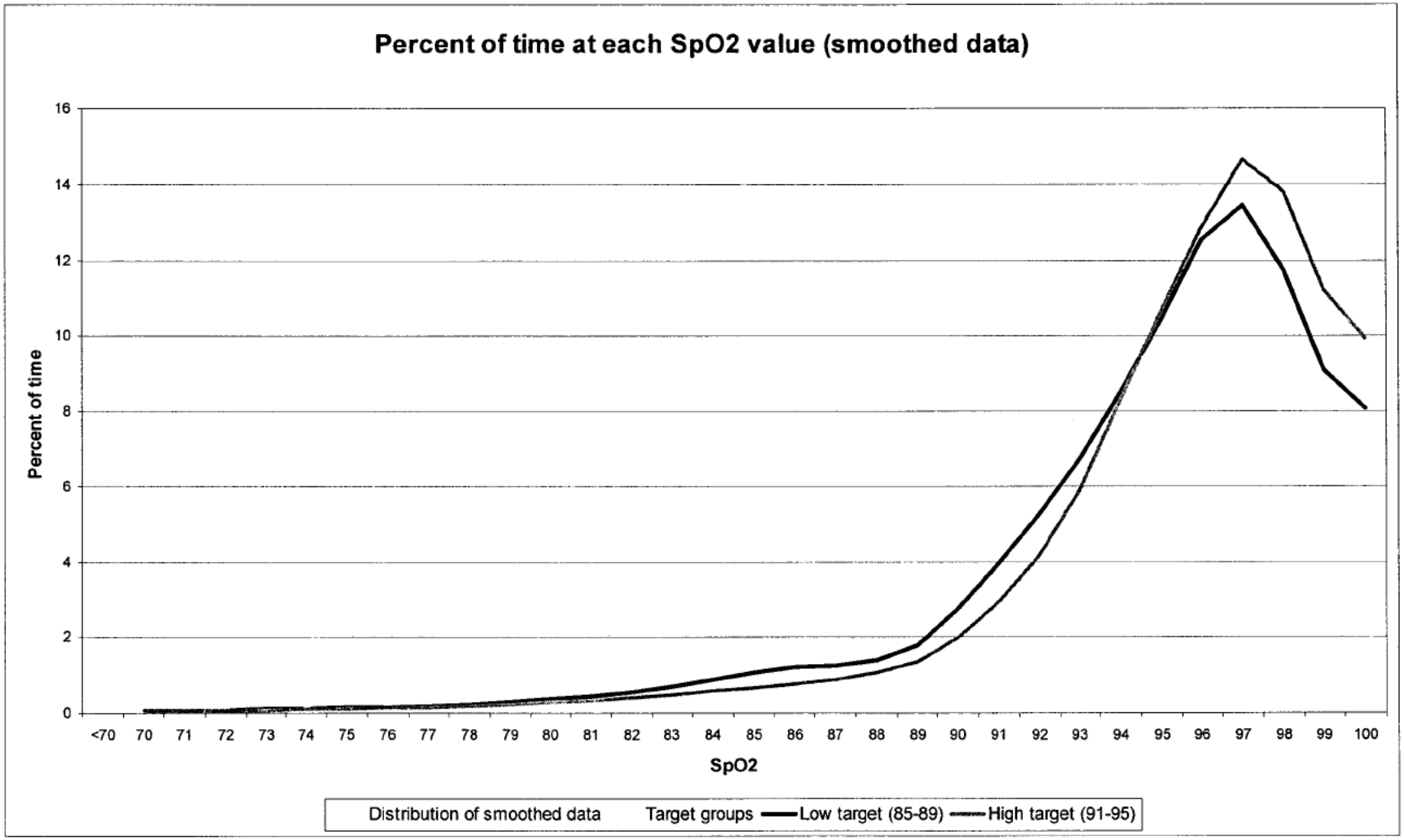
Range	High target (91-95)	Low target (85-89)
<84	2.93	3.46
>96	51.73	45.11

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.





From: Michele Walsh
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Donovan, Edward (DONOVAEF); Carlo, Wally; Duara, Shahnaz; Rich, Wade; Newman, Nancy
Subject: Updated DSMC slides
Date: Monday, January 16, 2006 4:46:31 PM
Attachments: DSMC Jan 14 2006MW suggestions.ppt

Neil:
Thanks again for all of your efforts. I went through your revised slides with my editor hat on: I have edited the style and format to make all similar. None of the content is changed: just the style of presentation in general to make it more simple and to use sub-bullets to help the data standout from the text.
Hope you find this helpful.
Michele
That which does not kill you, will make you stronger.
By the end of this,you should be Herculean in strength!

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 13, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving Oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became significantly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by > 9% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- **The optimal saturation range for ELBW is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Evidence for Currently used SpO2 Ranges is Lacking

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.**

Published Evidence

- **Sun et al compared units with upper limits of >95% with those of ≤ 95%**
  - (Ped Res 2002, 51:350A)
- **Tin et al reported units by the limits they set without any individual patient data.**
  - Arch Dis Child 2001;84:f106)

Published Evidence

- **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 practice changes including lowering the SpO2 limit – Did not provide actual data**

  -Chow et al, Pediatr 2003;111:339

- ***All of these observational studies suggested that lower SpO2 limits were associated with less ROP.***

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting this data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- **14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks**
- **Study performed to document practice prior to a trial with design parallel to SUPPORT**
- **Reported SpO2 limits ranged:**
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- **Median SpO2 in Hagadorn = 95%**
- **Median SpO2 from SUPPORT –**
  - All infants in trial = 92% and 94%
  - Infants in Oxygen = 91% and 93%
- **Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.**

Additional Evidence

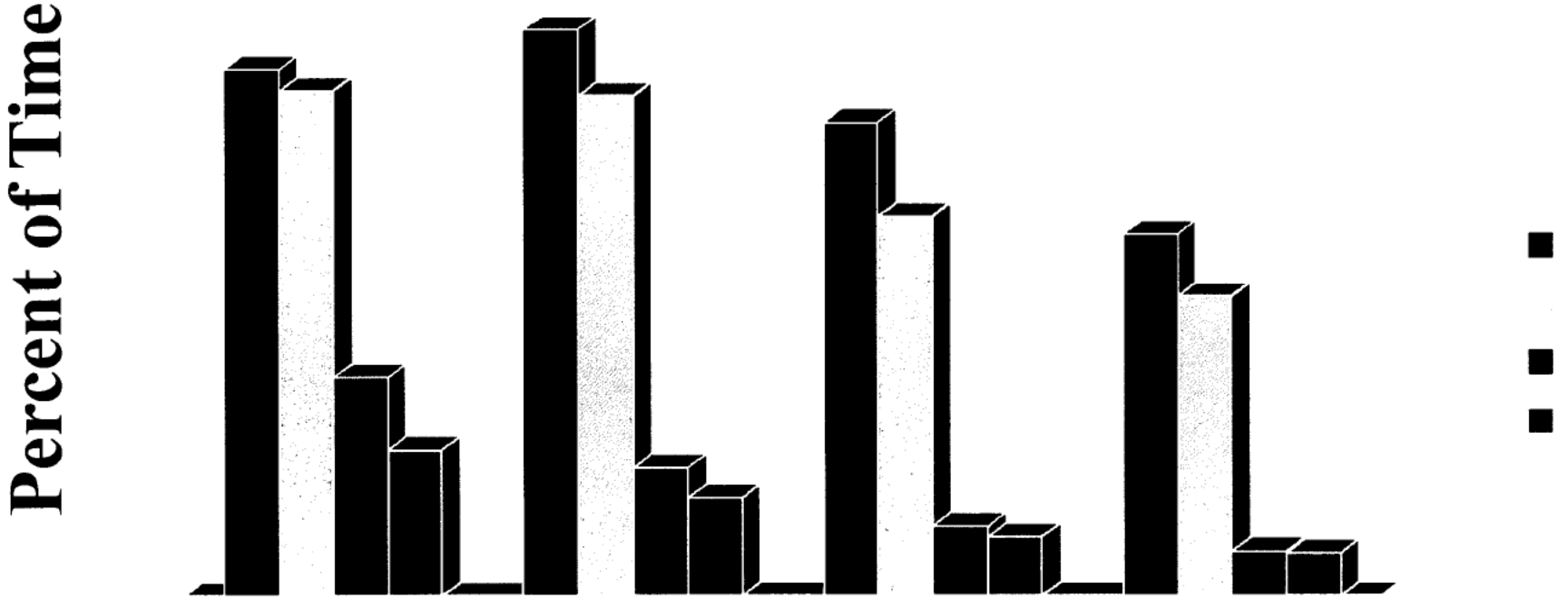
- **Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%**
- **Hagadorn study-**
  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants-**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW nonSUPPORT**
  51% time SpO2 > 95%

SpO2 values of SUPPORT infants in Room Air

- **Infants in room air had a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.**

	91%- 95% Group	85% - 89% Group
Room Air	**52.7%**	**46.1%**
Oxygen	**12.6%**	**9.4%**

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



Impact of the Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in inability to create a whole value for each displayed value.**
- **The study oximeters display and save values which are altered for SpO2 readings of > 84% to < 96%**
- **These displayed values are transmitted to RTI.**
- **This data can be analyzed without applying any correction for the altered values, and this is done to provide feedback to the sites regarding the % of time in range.**

Impact of Algorithm

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Impact of Algorithm

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%
- Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.
- This incorrectly assigned infants in RA to oxygen group.

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% while receiving oxygen.**
- **Previous analyses overstated the exposure.**
- **Most of the overestimate was from misclassification of infants in partial oxygen.**

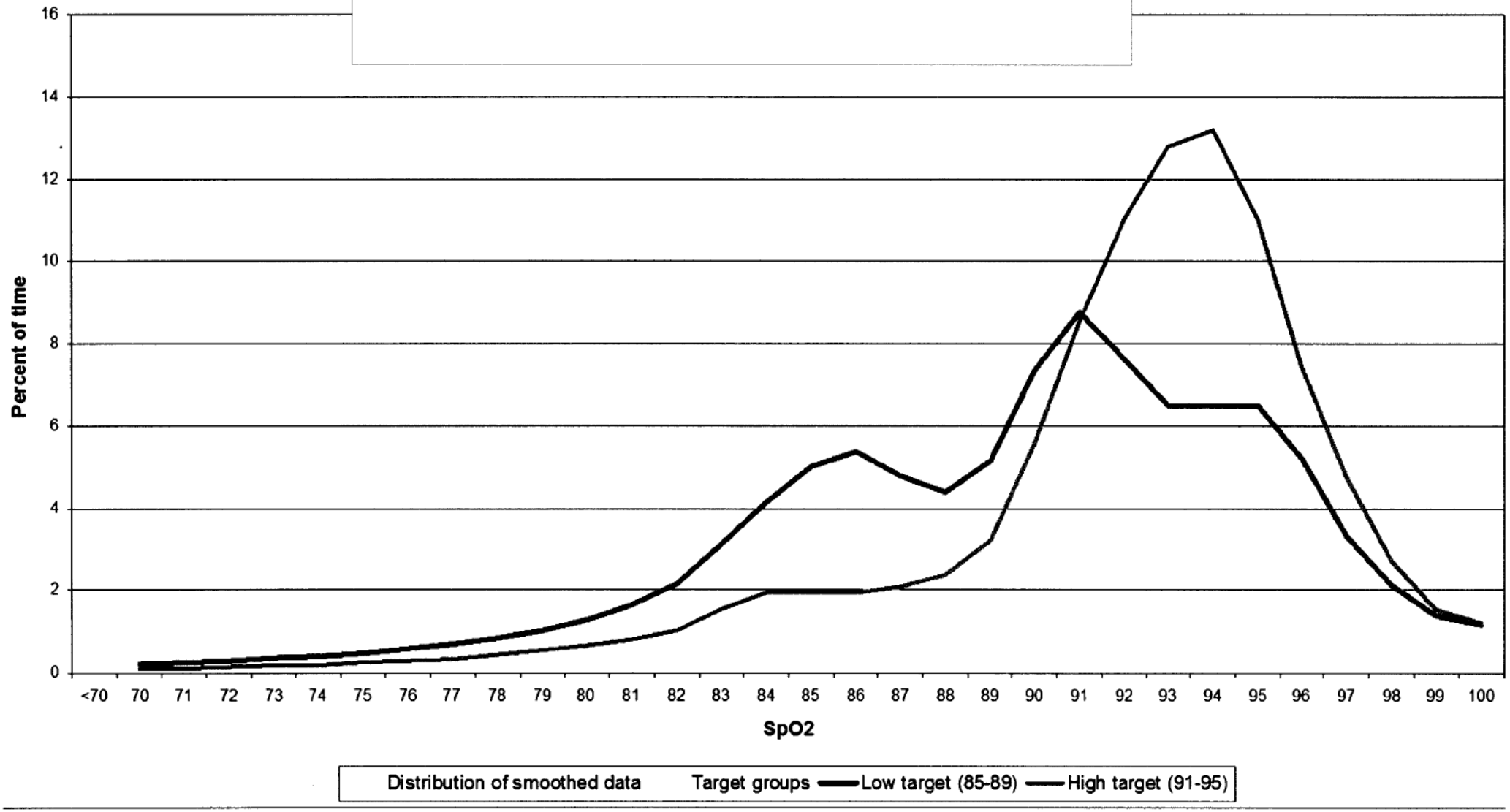
Safety Issue of SpO2 > 95%

- **This trial will help to determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**

DSMC pt 2: Futility regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - Mean all infants– 90% vs 92%
  - Median all infants– 92% vs 94%
  - Median infants in oxygen at all 3 data points- 91% vs 93%
- **Time with an SpO2 of ≤90% shows a difference of > 24%**
  - 91% - 95% Group 22.8%
  - 85% - 89% Group 47.6%

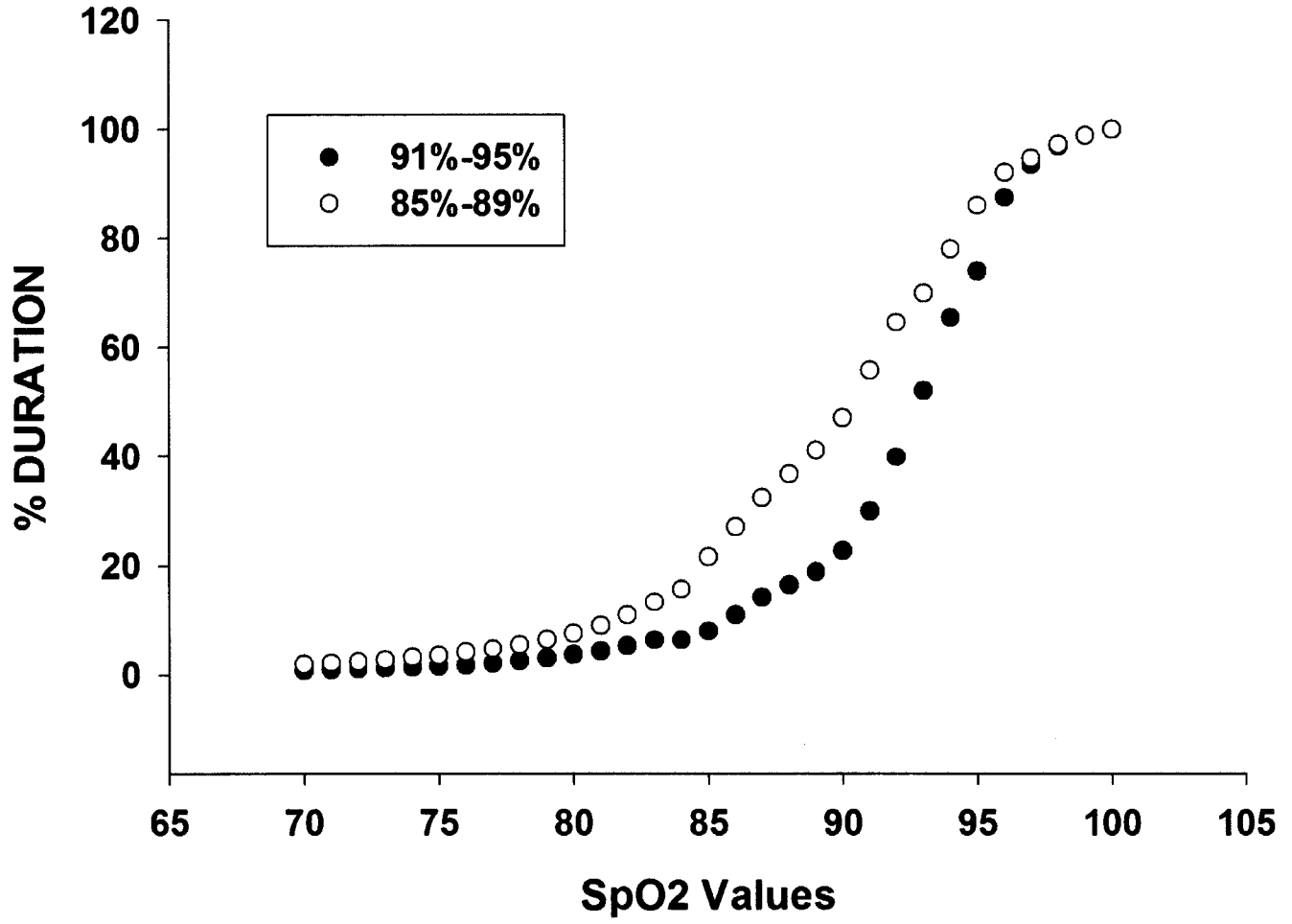
Based on Oxygen Days



Slide 25

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



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**

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - 91%-95% group 26.6%
  - 85%-89% group 35.5%
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Conclusion

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

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"
Date:	Saturday, January 14, 2006 8:16:26 PM
Attachments:	DSMC Jan 14 2006.ppt

Hi Everyone
I have tried to incorporate all the ideas from the meeting. There are more slides because I made them less crowded. They will not take longer to present. I also added an explanation (slide 14 I think) about room air so that the non MDS would understand why room air is an issue.
I would appreciate your thoughts.
I think this presentation can be done in about 20 minutes and we can use the discussion time to further explain any issues.
I have removed all the titles which indicated DSMC response.
I feel that we are in good shape to justify the continuation of SUPPORT.
Regards
Neil Finer

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 13, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving Oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became significantly shorter**

Summary of Responses

- ✓ **We have a degree of separation between the oximeter groups for exposures to SpO2 values of above or below 90%**
- ✓ **The oximeter groups differ by > 9% in their durations in room air, in the expected direction**

The 85%-89% Group spend more time in Room Air

- ✓ **We can do better and will present plans to improve both separation and durations of elevated SpO2s**

Evidence for Current SpO2 Ranges

- **The appropriate durations of exposure to different levels of SpO2 is not currently known.**
- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**

Evidence for Current SpO2 Ranges
Lack of Relevant data

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **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 targets were adhered to.**

Evidence for Current SpO2 Ranges

- Sun et al compared units with upper limits of >95% with those of ≤ 95% (Ped Res 2002, 51:350A)
- Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)

Evidence for Current SpO2 Ranges
Lack of Relevant data

- **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 is unique and will provide this information based on a large prospective cohort**
- **This trial is 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.**

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)**
- ✓ **There were 14 centers from 3 countries who provided patient data**
- ✓ **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%**

Safety Issue of SpO2 > 95%

- ✓ **Median SpO2 from Hagadorn study = 95%, thus these infants spend approximately 50% of the time with an SpO2 > 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94% overall, and 91% vs 93% for infants in oxygen for the entire day.**

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, not enrolled in SUPPORT – SpO2 > 95% for > 50% time
- The current available experience both within the NRN and from other reporting units suggests that ELBW infants currently spend approximately 50% of the time with SpO2s > 50%

Safety Issue of SpO2 > 95%

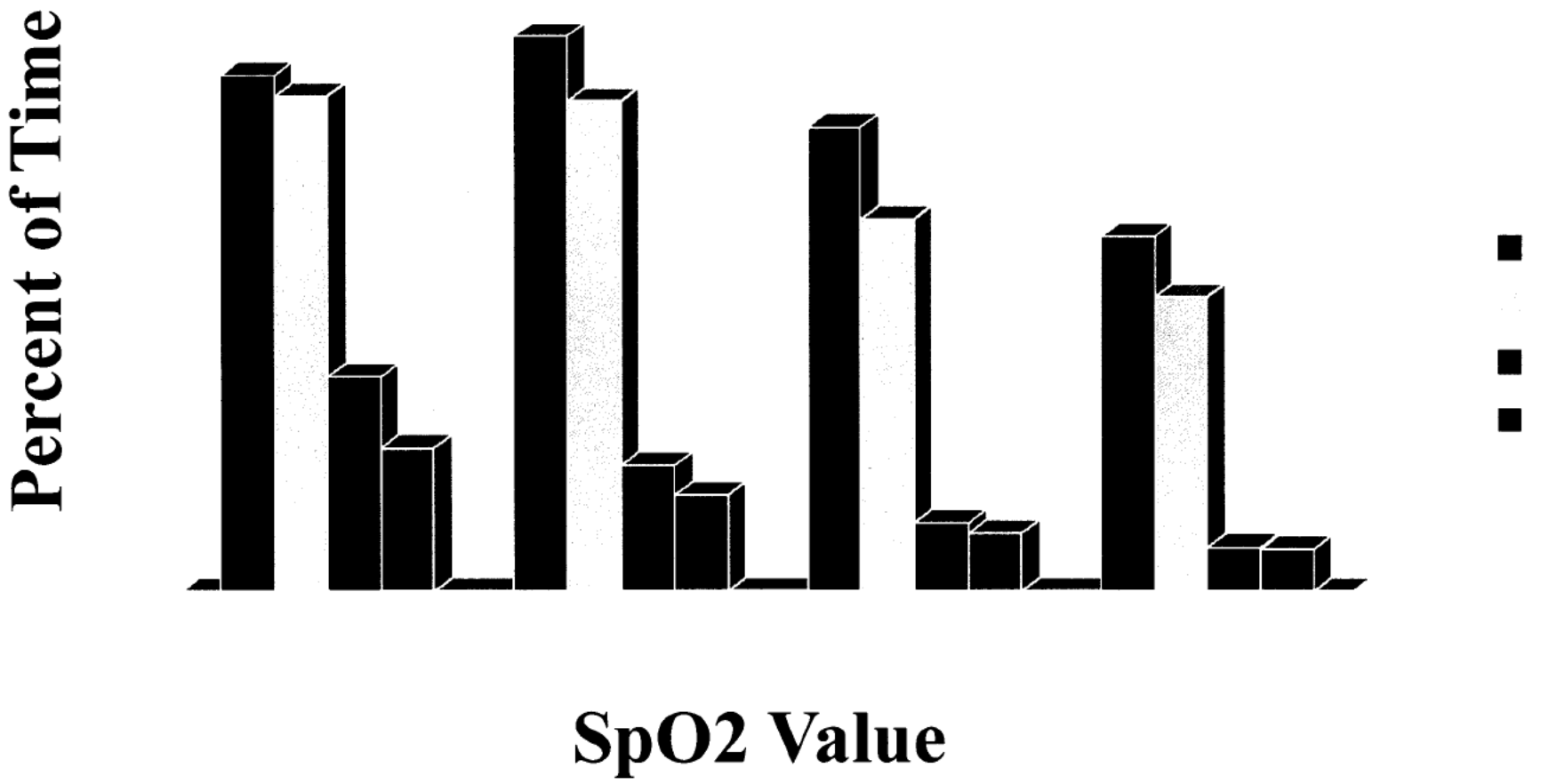
- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time
- Median SpO2 in healthy preterm infants in room air = 97% (Ng et al Arch Dis Child 1998;79:F64)
- Infants in room air can not have changes made to their inspired oxygen to lower their SpO2s.

SpO2 values of trial infants in Room Air SUPPORT Data

- **Infants in room air had approximately a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.**

	91%- 95% Group	85% - 89% Group
Room Air	**52.7%**	**46.1%**
Oxygen	**12.6%**	**9.4%**

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



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 study oximeters display and save values which are altered for SpO2 readings of > 84% to < 96%
- These values which are part of each infants data set are transmitted to RTI as a part of the study.
- This data can be analyzed without applying any correction for the altered values, and this is done to provide feedback to the sites regarding the % of time in range.

Safety Issue of SpO2 > 95%

- To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.
- The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.

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 subsequent analyses for durations > 96% and < 84% as these are values which do not require conversion and are always unaltered.**

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.

Safety Issue of SpO2 > 95%

- ✘ The initial analyses assigned an infant to oxygen if they received any oxygen that day.
- ✓ 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%

Safety Issue of SpO2 > 95%

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Safety Issue of SpO2 > 95%

Further analyses including only infants on Oxygen at all 3 data points for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95%

- **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 are significantly lower than the original data reviewed by the 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% while receiving oxygen, based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **The majority of the overestimate was from assuming that infants analyzed as being on oxygen for a day were actually receiving oxygen for the entire day**

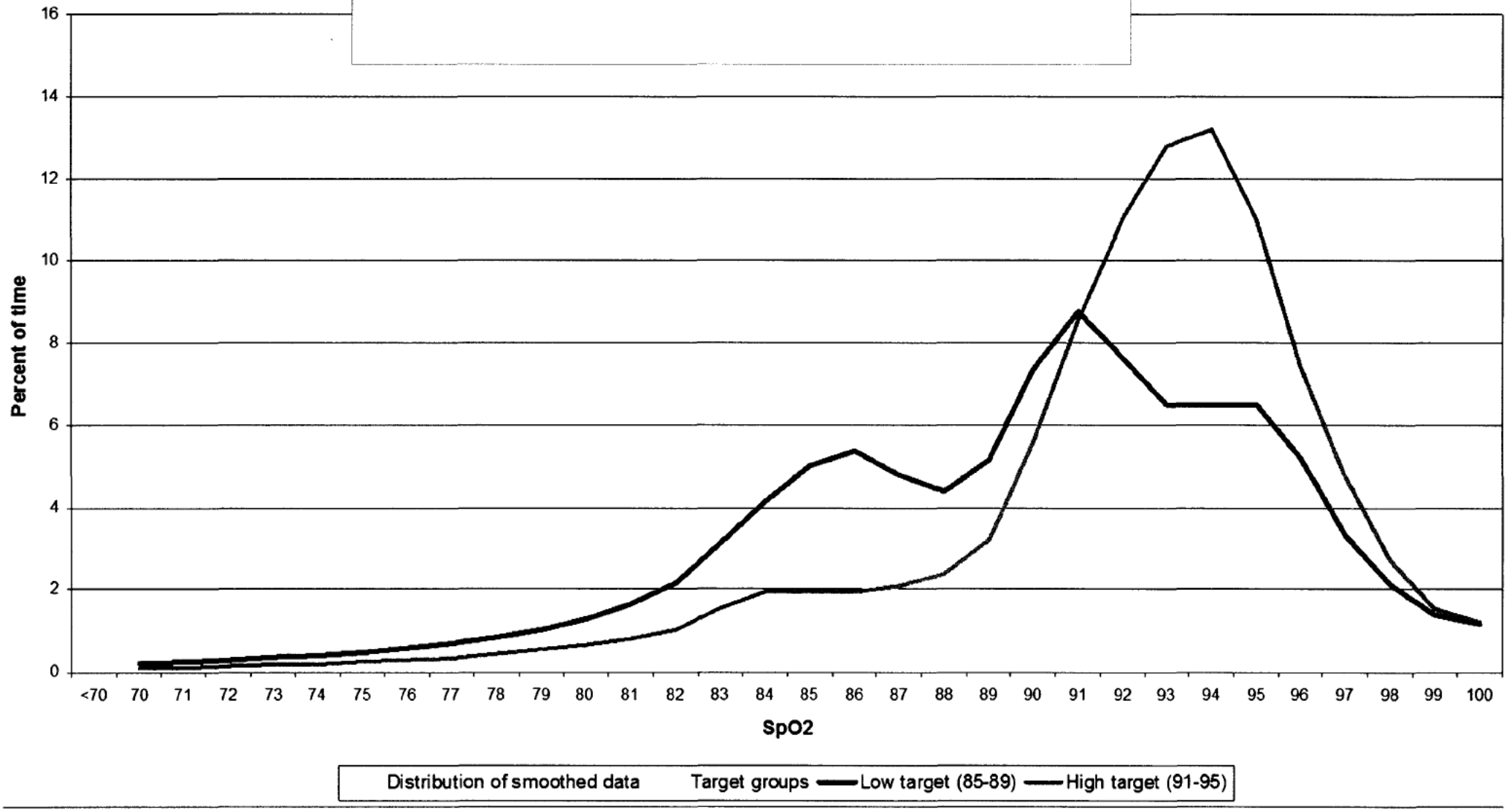
Safety Issue of SpO2 > 95%

- **This trial will help to determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**

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 infants who received 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)**

Based on Oxygen Days



Slide 28

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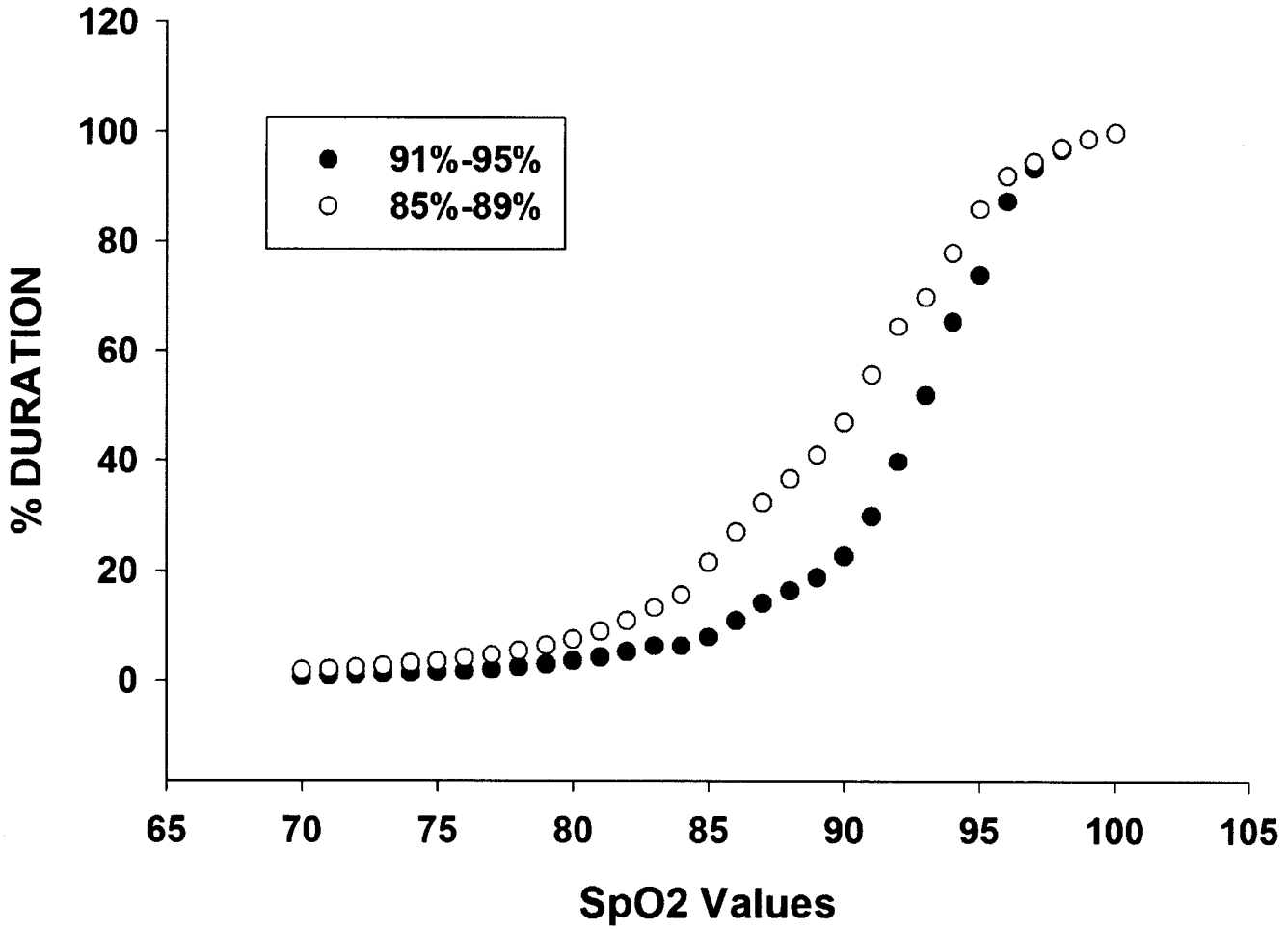
Pediatrics, 12/16/2005

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



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

Separation of Oximeter Groups

- **The time spent in Room Air during the first 14 days of life was 26.6% for the 91%-95% group compared to 35.5% for the 85%-89% group.**
- **These differences persisted for data beyond 14 days**

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.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 whether the infant was receiving Oxygen or room air.

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
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Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Conclusion

- **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: Brenda Poindexter
To: Sood, Beena; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: IPGE
Date: Friday, January 13, 2006 8:33:30 AM

Beena,
Just to follow-up from the meeting, our vote from Indiana would be as Greg outlines below. Thanks, Brenda

------ Forwarded Message
From: Greg Sokol <gsokol@iupui.edu>
Date: Wed, 11 Jan 2006 18:09:32 -0500
To: Brenda Poindexter <bpoindex@iupui.edu>
Subject: IPGE

Brenda,

Beth stated that running the infusion rate at 4 ml/hr provided good aerosol delivery immediately and nearly continuously if primed with 2 ml.

Our trials with 4 ml/hr with only 5 drops as a prime provided negligible delivery for the first 30 minutes. This became nearly continous after ~ 1 hour.

Based on these observations, I would be comfortable that we are delivering study drug continuously (at least 90% of the time) by using the 4 ml/hr infusion rate with a 2 ml prime.

On conventional ventilation, I would favor injection 20 cm upstream from the wye (ETT connect) to allow for better mixing (I believe Krisa will support this). On HFOV, connection at the ETT connect appears to be best. Greg

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"
Date:	Thursday, January 12, 2006 10:31:13 PM
Attachments:	DSMC Jan 12 revised2006.ppt

A few more changes
Sleep tight
Neil

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 11, 2006

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."

Summary of Responses

- **Alarm limits were those used by NRN members**
- **Displayed SpO2 values < 84% and > 96% would represent the actual SpO2**
- **Infants in RA have significantly higher SpO2 values than infants receiving Oxygen especially > 96%**

Summary of Responses

- **If an infant was assumed to be in oxygen but was actually in RA, the duration of the SpO2 > 96% would be excessive compared to an infant actually receiving Oxygen.**
- **The initial analyses did not sufficiently distinguish whether the infant was on Oxygen or not as they were based on the highest value for the day.**

Summary of Responses

- **Repeat analyses including only infants known to have been on oxygen at all 3 daily FiO2 recordings reduced the overestimates of elevated SpO2 values**
- **We have achieved some separation between the oximeter groups for exposures to SpO2 values of above or below 90%**

Summary of Responses

- **The oximeter groups differ by > 9% in their durations in room air, in the expected direction**

The 85%-89% Group spend more time in Room Air

- **We can do better and will present plans to improve both separation and durations of elevated SpO2s**

Evidence for Current SpO2 Ranges

- **The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.**
- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**

Evidence for Current SpO2 Ranges Lack of Relevant data

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- **Tin et al reported units by the limits they set without any individual patient data (Tin et al Arch Dis Child 2001;84:F106)**
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- **All of these studies suggested that lower SpO2 limits were associated with less ROP.**

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- **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**
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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)**
- ✓ **There were 14 centers from 3 countries who provided patient data**
- ✓ **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%**

Response to DSMC

Safety Issue of SpO2>95%

- ✓ **Median SpO2 from Hagadorn study = 95%, thus these infants spend approximately 50% of the time with an SpO2 > 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94% overall, and 91% vs 93% for infants 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, not enrolled in SUPPORT – SpO2 > 95% for > 50% time
- The standard of care experience both within the NRN and from other reporting units suggests that ELBW infants currently spend approximately 50% of the time with SpO2s > 50%

Response to DSMC:
Safety Issue of SpO2 > 95%

- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time
- Median SpO2 in healthy preterm infants in room air = 97% (Ng et al Arch Dis Child 1998;79:F64)

SpO2 values of trial infants in Room Air SUPPORT Data

- **Infants in room air had approximately a > *four fold* increase in the time spent at higher SpO2 durations when compared with infants receiving oxygen.**
- **For SpO2 values > 96%, the cumulative values are shown below and the increased durations at high SpO2s appears equivalent for the 2 target ranges:**

	91%- 95%	85% - 89%
Room Air	**52.7%**	**46.1%**
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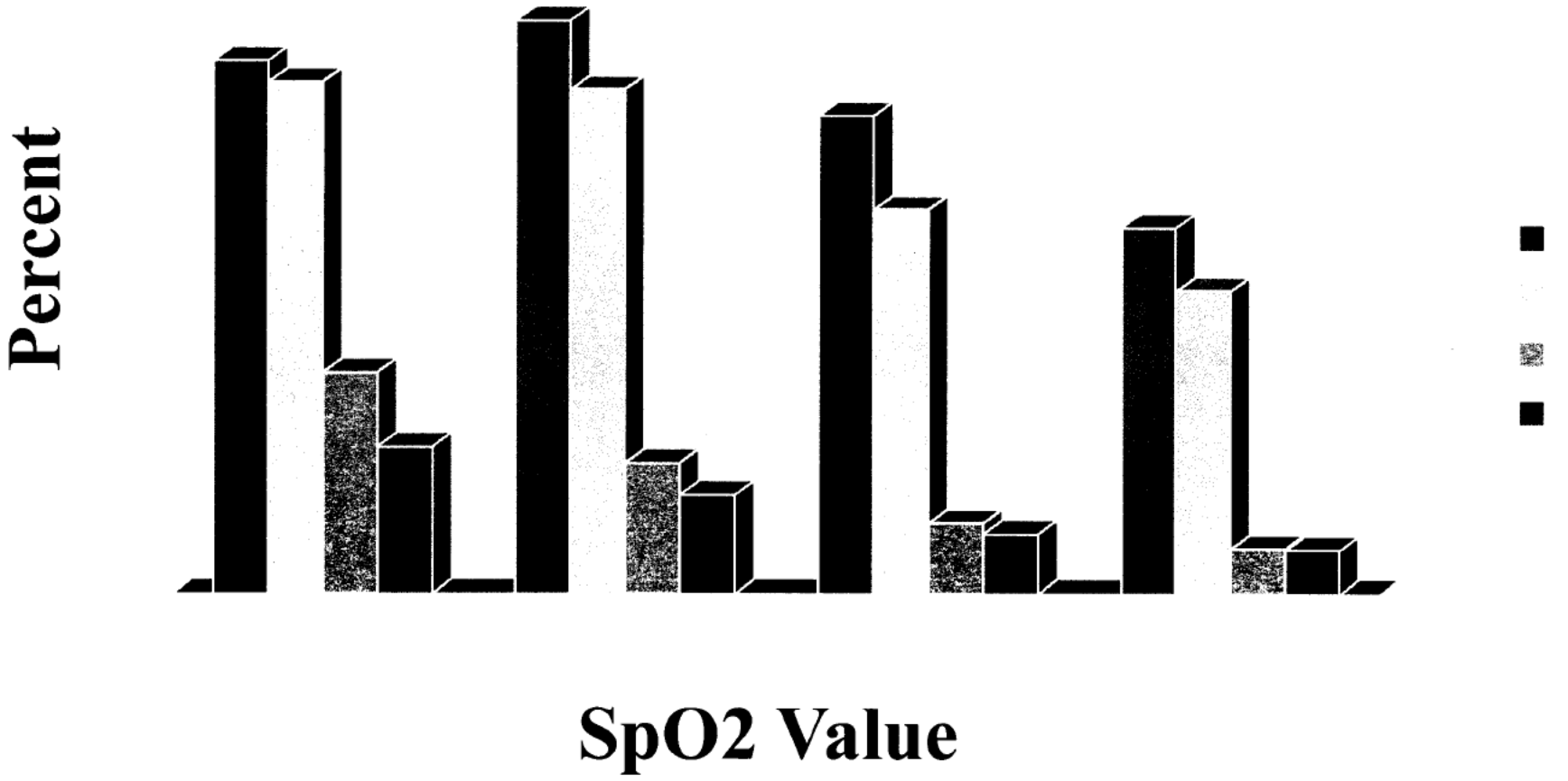
Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial



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 study oximeters display and save values which are altered for SpO2 readings of > 84% to < 96%
- These values which are part of each infants data set are transmitted to RTI as a part of the study.
- This data can be analyzed without applying any correction for the altered values, and this is done to provide feedback to the sites regarding the % of time in range.

Response to DSMC: Safety Issue of SpO2>95%

- To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.
- The effect of time in room air was not initially appreciated

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%
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- ✘ The initial analyses assigned an infant to oxygen if they received any oxygen that day.
- ✓ 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%

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Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial 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%

- **Further analyses including only infants on Oxygen at all 3 data points for a given day for the first 14 days of life**

(Subsequent 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%

- **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.**
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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 infants who received 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)**

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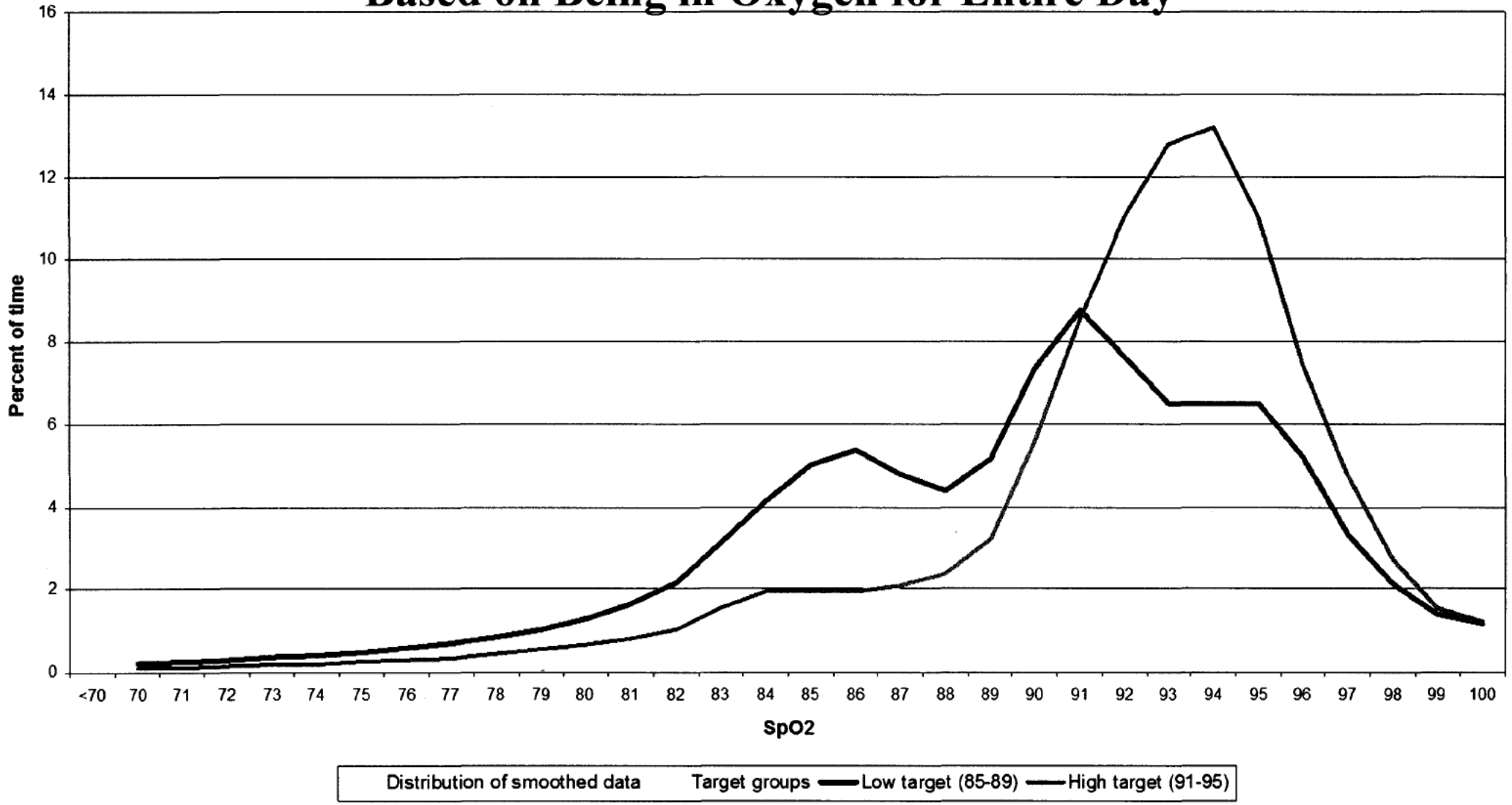
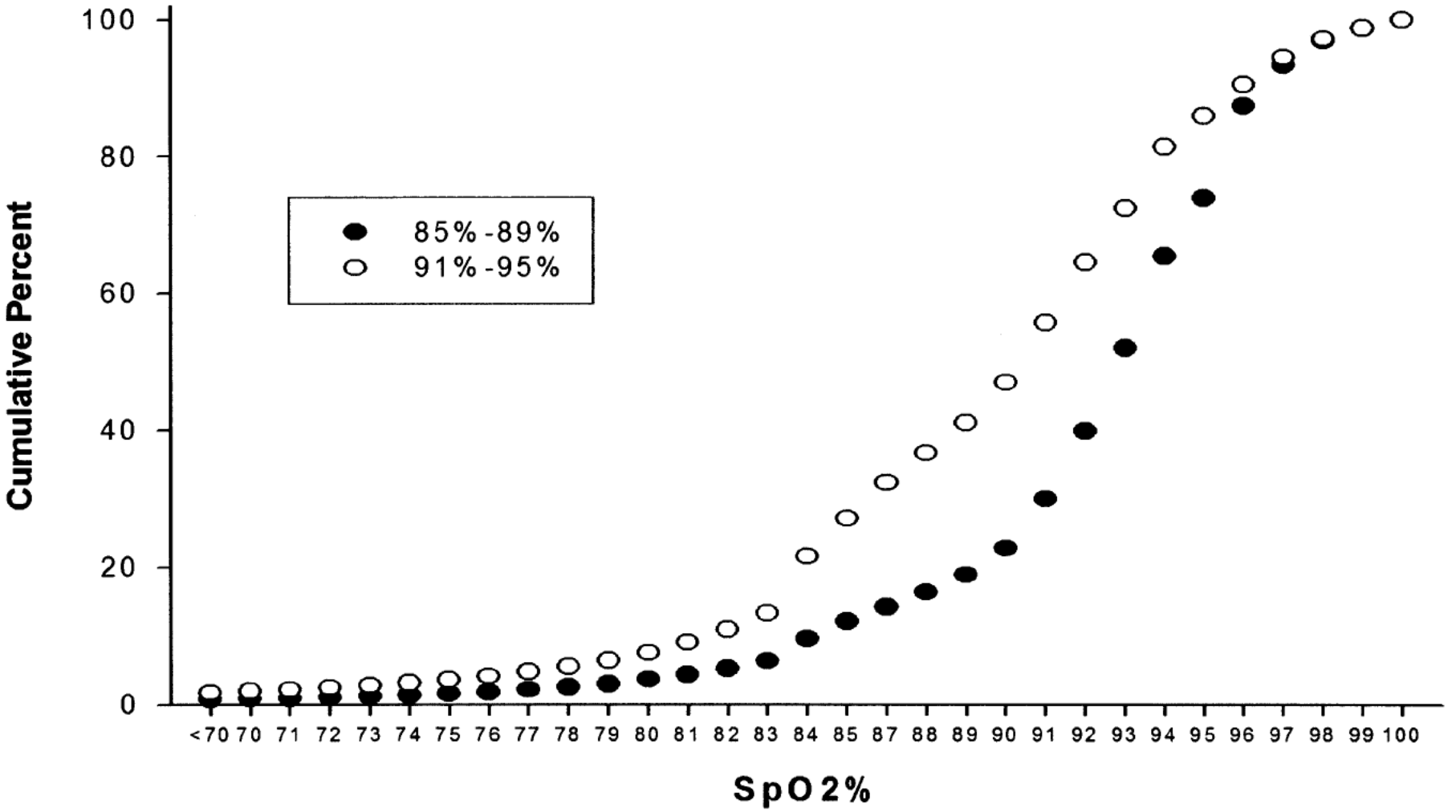


Slide 28

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

Cumulative SpO2 Durations for Oximetry Groups



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- **We examined the FiO2 requirement of the infants in the Oximeter arms.**
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- **These differences persisted for data beyond 14 days**

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4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

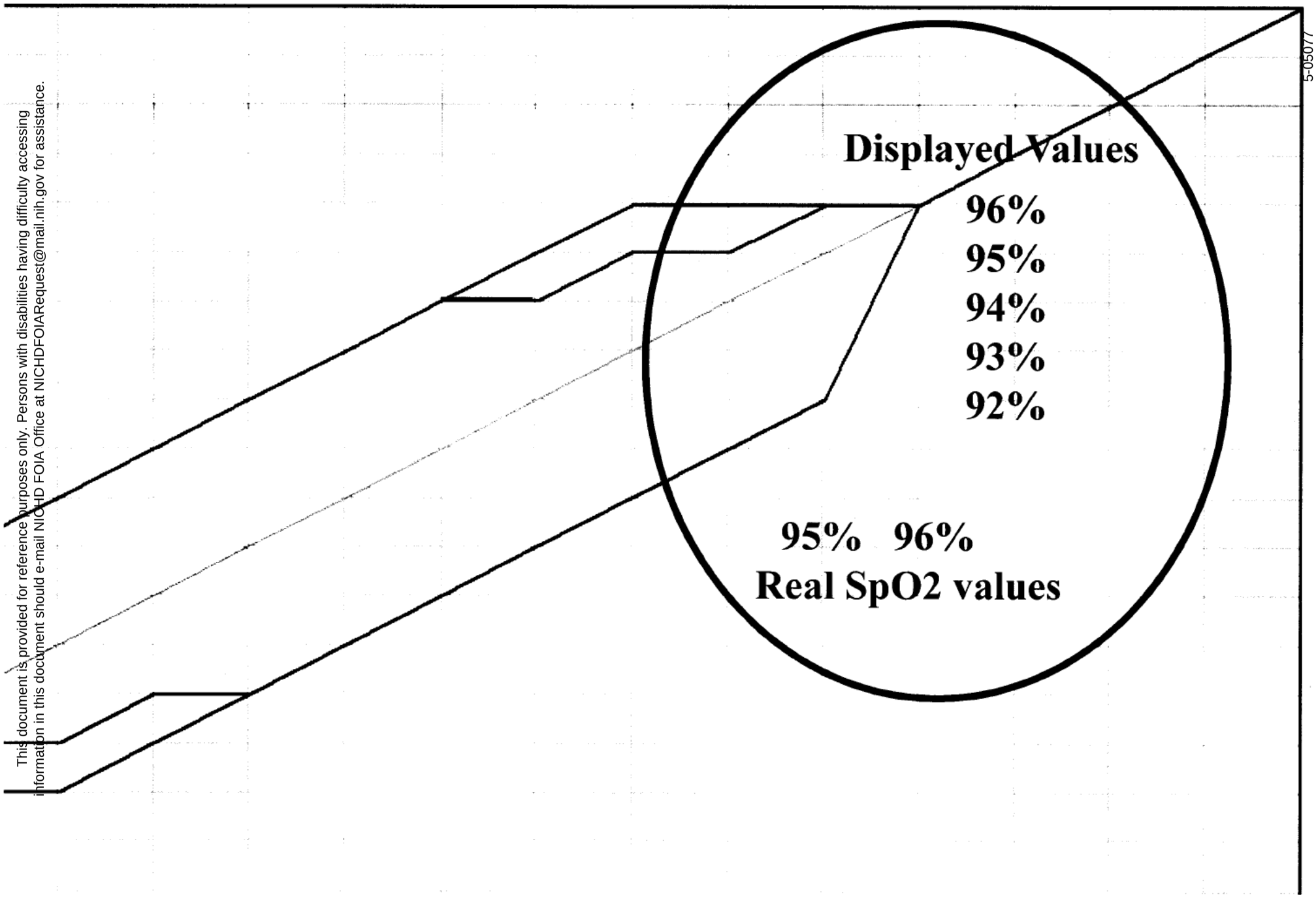
Response to DSMC:

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. 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.**



5-05077

Response to DSMC: Safety Issue of SpO2>95%

- The data evaluated by the DSMC had an overestimation of durations > 95% due to rounding 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

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"
Subject:	FW:
Date:	Thursday, January 12, 2006 9:23:28 PM
Attachments:	DSMC Jan 12 2006.ppt

Hi Everyone
Here is the next version. Please send me any changes. I will present the changes tomorrow
Neil

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, January 12, 2006 3:54 PM
To: 'Carlo Waldemar (E-mail)'; wrich@ucsd.edu; Maynard Rasmussen
Cc: nfiner@ucsd.edu
Subject:

Wally, Wade and Maynard
Please look this over and see if it is an improvement
Neil

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

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Jan 11, 2006

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- **The initial analyses did not sufficiently distinguish whether the infant was on Oxygen or not as they were based on the highest value for the day.**
- **Repeat analyses including only infants known to have been on oxygen at all 3 daily FiO2 recordings reduced the overestimates of elevated SpO2 values**
- **The conversion algorithm also contributed to an overestimate of high SpO2 durations, but to a lesser extent.**

Summary of Responses

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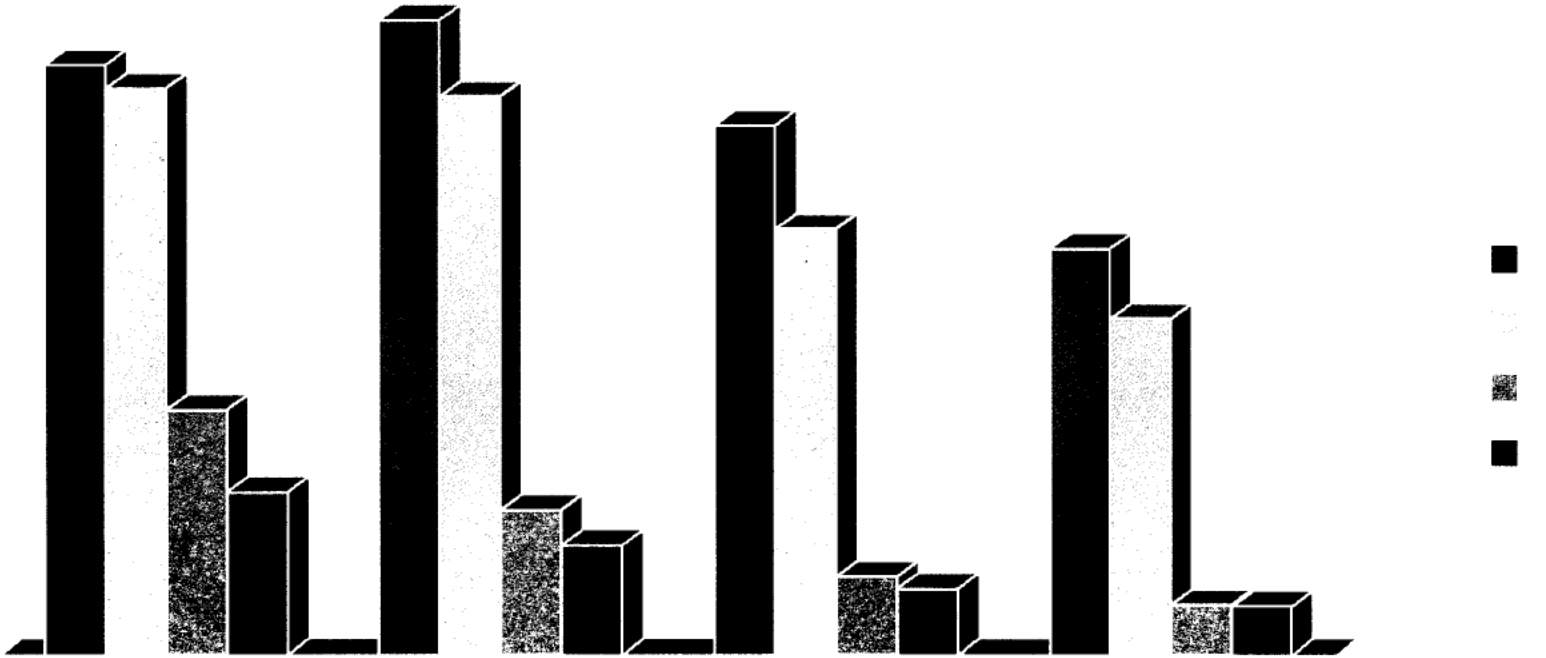

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- To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.
- The design of the algorithm used in the study results in an SpO2 of 88% to 92% being displayed when the actual SpO2 is 91% to 95% for the High Target Group
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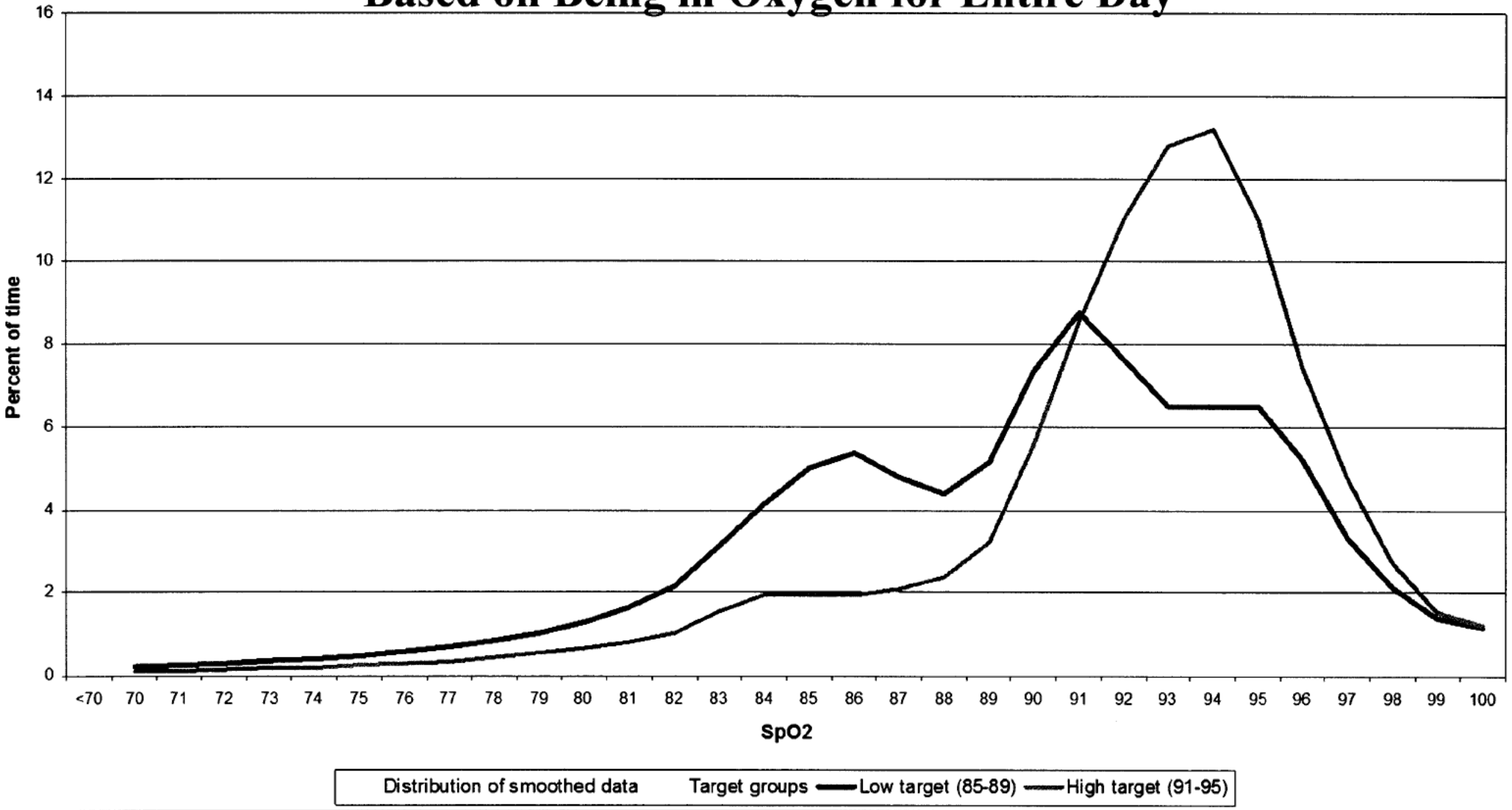

Slide 25

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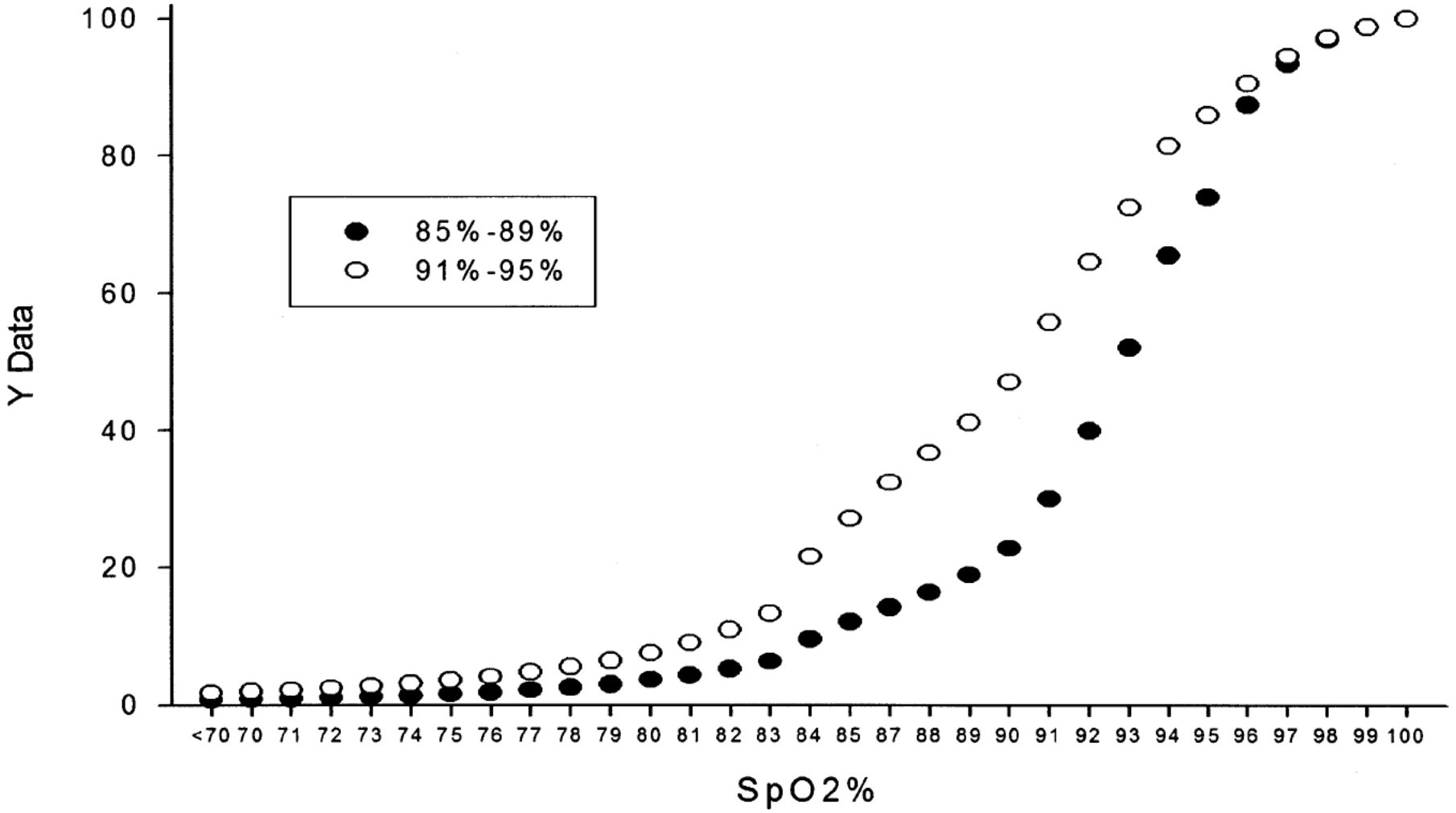
Pediatrics, 12/16/2005

5-05105

Cumulative SpO2 Durations for Oximetry Groups



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- **These differences persisted for data beyond 14 days**

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- **The time in Target using only days when infants are in oxygen for all 3 data points for the first 14 days of life**

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

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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.**
8. **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.**

Response to DSMC: Safety Issue of SpO2>95%

- **The data evaluated by the DSMC had an overestimation of durations > 95% due to rounding 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**

From:	Wally Carlo, M.D.
To:	nfiner@ucsd.edu; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Dale_Phelps@URMC.Rochester.edu
Cc:	Avroy A. Fanaroff, M.D.; Hastings, Betty J.; Ed Donovan; Poole, W. Kenneth; Maynard Rasmussen; Michele; Shahnaz Duara; Wade Rich; Gantz, Marie
Subject:	RE: SUPPORT response comments
Date:	Wednesday, January 11, 2006 2:21:16 PM

Neil: Sorry for my delayed comments. I agree with Abhik that the amount of info is substantial. I also worry that the message may be lost. I will bring to the meeting my specific suggestions you may want to consider. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, January 11, 2006 10:19 AM
To: 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Dale_Phelps@URMC.Rochester.edu
Cc: 'Avroy A. Fanaroff, M.D.'; 'Hastings, Betty J.'; 'Ed Donovan'; 'Poole, W. Kenneth'; 'Maynard Rasmussen'; 'Michele'; 'Shahnaz Duara'; Wade Rich; Wally Carlo, M.D.; 'Gantz, Marie'; 'Neil Finer'
Subject: RE: SUPPORT response comments

Abhik
Many thanks for your suggestions. I am also worried about the number analyses that we ran - but the option was to the stop the trial.
In addition while rounding accounts for a portion of the perceived SpO2 durations > 95%, in fact it is the contamination of infants presumed to be on oxygen who are in room air which contributes a much greater proportion of the high SpO2 values. The first analyses using infants only in oxygen reduced the duration from 36% down to 21%. The second analyses, using only in oxygen for all 3 time points further reduced this to 12%. We did however use > 96% for our analyses. Thus the actual duration when using only in oxygen for all 3 time points was 1/3rd of what the original measure.
I have incorporated your suggestions.
Many thanks again
Neil

-----Original Message-----
From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, January 11, 2006 6:20 AM
To: nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Dale_Phelps@URMC.Rochester.edu
Cc: Avroy A. Fanaroff, M.D.; Hastings, Betty J.; Ed Donovan; Poole, W. Kenneth; Maynard Rasmussen; Michele; Shahnaz Duara; Wade Rich; Wally Carlo; Gantz, Marie
Subject: RE: SUPPORT response comments

Neil:

Here are a few comments from myself and Marie:

1. In slide 10, for the Case Western data, it should be made explicit that these kids are not in any trial and thus represent standard clinical practice.
2. In slide 15, I would avoid saying "rounding errors" (the term

'errors' may raise unnecessary flags); maybe say "peculiarities of the rounding algorithm" or something to that effect.
3. In slides 20 and 26 it should probably be clarified that these analyses only include the first 14 days of life.

In general I worry a bit that in building our case, specially for the safety issue, we may be presenting the DSMC with too much information. As I see it, the main points for the safety issue are (a) current literature has nothing to suggest that these levels are unsafe, and (b) the rounding algorithm made things look significantly worse than they actually are. That focus seems to get a bit diffused among all the information presented. I also worry that this will make the DSMC think that we have done a tremendous amount of analyses (which we have), having adverse consequences on significance levels/p values observed later on, if the trial were to resume. (It should not, because we have not done any formal testing, but the perception may be there.) It also may be too much to cover in 20 minutes.

Thanks

Abhik

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From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, January 09, 2006 1:48 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Dale_Phelps@URMC.Rochester.edu
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: RE: SUPPORT response comments

Hi Dale
Thanks for the detailed analysis. We have made a number of changes as per your suggestions, and had also designed another graph.
I am enclosing the newer version. Please be as critical at the Steering Comm SUPPORT meeting. We only have 20 minutes to present to the DSMC.
Many thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, January 09, 2006 7:52 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT response comments

Neil
Please look at these suggestions from Dale.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Sun Jan 08 21:45:48 2006

Subject: RE: SUPPORT response comments

<<Response to DSMC.doc>>

Hi Rose,
my comments, will try to send to neil in the am when I get to my desk.
Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
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); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Betty Hastings
Sent: 1/5/2006 8:00 AM
Subject: SUPPORT

HI,

Attached is a PowerPoint presentation which Dr. Finer has prepared for the DSMC open meeting which will be held on January 24 in Rockville. He will present this in brief at the steering committee meeting. If you have comments, please send them.

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>

<<SUPPORT Trial Final DSMC Response - Jan 3.ppt>>

From:	Neil Finer
To:	nfiner@ucsd.edu; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; Dale_Phelps@URMC.Rochester.edu
Cc:	"Avroy A. Fanaroff, M.D."; "Hastings, Betty J."; "Ed Donovan"; "Poole, W. Kenneth"; "Maynard Rasmussen"; "Michele"; "Shahnaz Duara"; "Wade Rich"; "Wally Carlo"; "Gantz, Marie"
Subject:	RE: SUPPORT response comments
Date:	Wednesday, January 11, 2006 1:31:09 PM
Attachments:	SUPPORT Trial Final DSMC Response - Jan 11.ppt

Hi Everyone
Here is the most current version that I will present tomorrow morning.
Safe travels.
Neil

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From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, January 11, 2006 8:19 AM
To: 'Das, Abhik'; 'Higgins, Rosemary (NIH/NICHD) [E]';
Dale_Phelps@URMC.Rochester.edu
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<<SUPPORT Trial Final DSMC Response - Jan 3.ppt>>

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 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

- **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)**
- ✓ **There were 14 centers from 3 countries who provided patient data**
- ✓ **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%**

Response to DSMC

Safety Issue of SpO2>95%

- ✓ Median SpO2 from Hagadorn study = 95%
- ✓ Medians from SUPPORT Oximeter groups – 92% and 94% overall, and 91% vs 93% only for infants in oxygen for the entire day.

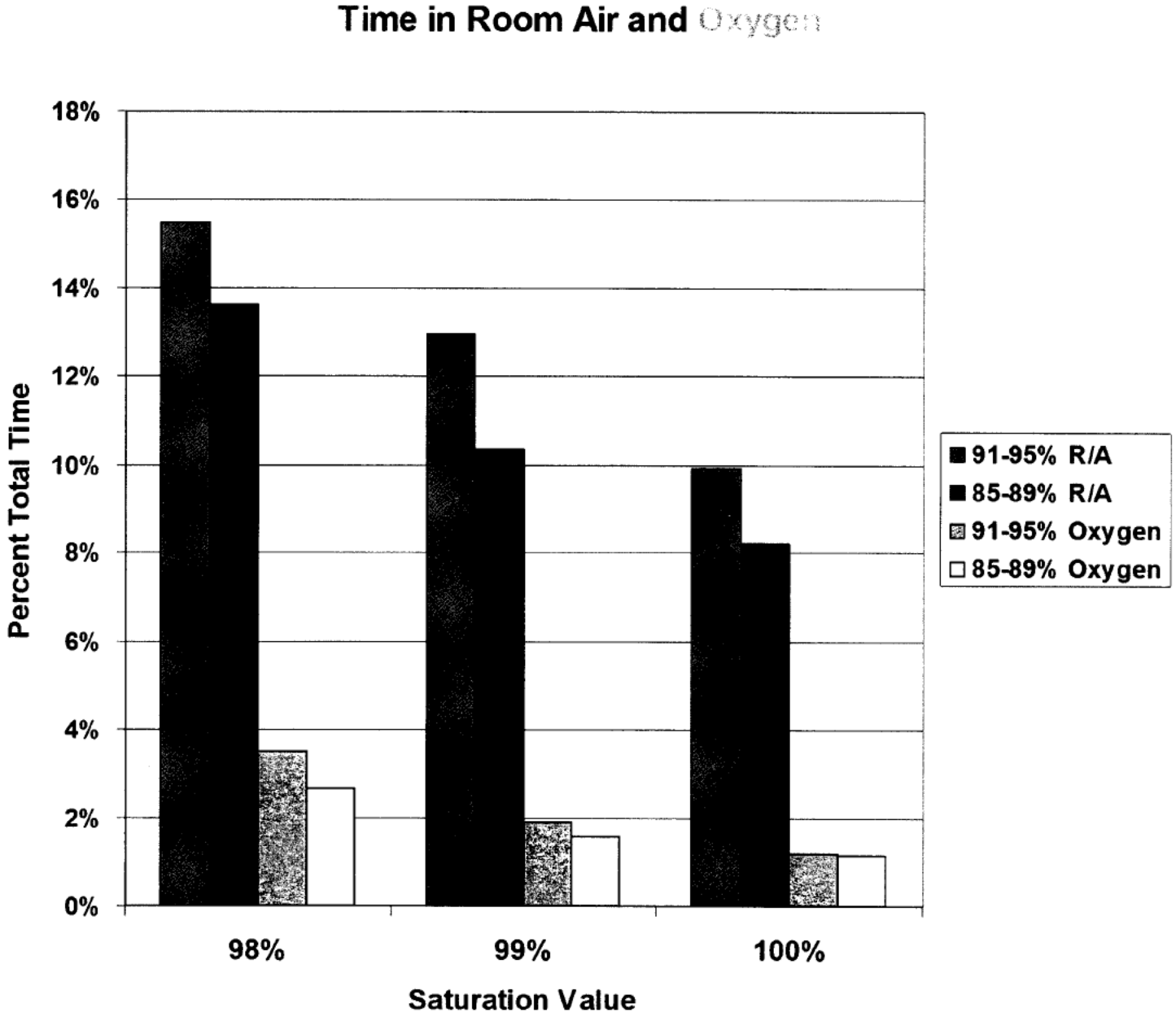
Response to DSMC:
Safety Issue of SpO2>95%

- STOP-ROP high treatment infants spent 97% of time > 95%
- Case Western a current NRN Center – Current data from SUPPORT type ELBW infants, not enrolled in SUPPORT – SpO2 > 95% for > 50% time
- SUPPORT Infants on room air – SpO2 > 95% from 46% to 69% of time

SpO2 values of trial infants in Room Air

- **Infants in room air had approximately a *six fold* increase in the time spent at higher SpO2 durations**
- **For SpO2 values > 97%, the cumulative values are shown below and the increased durations at high SpO2s appears equivalent for the 2 target ranges:**

	91%- 95%	85% - 89%
Room Air	**38.3%**	**32.2%**
Oxygen	**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 study oximeters display and save values which are altered for SpO2 readings of > 84% to < 96%
- These values which are part of each infants data set are transmitted to RTI as a part of the study.
- This data can be analyzed without applying any correction for the altered values, and this is done to provide feedback to the sites regarding the % of time in range.

Response to DSMC: Safety Issue of SpO2>95%

- To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.
- The design of the algorithm used in the study results in an SpO2 of 88% to 92% being displayed when the actual SpO2 is 91% to 95% for the High Target Group
- As a result, when the actual SpO2 increases above 95%, the study oximeter will rapidly change from 93% to 96% or greater for this group.

Response to DSMC: Safety Issue of SpO2>95%

- The data evaluated by the DSMC had an overestimation of durations > 95% due to rounding 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% for the first 14 days of life (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%

- **Further analyses including only infants on Oxygen at all 3 data points for a given day for the first 14 days of life**

(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%

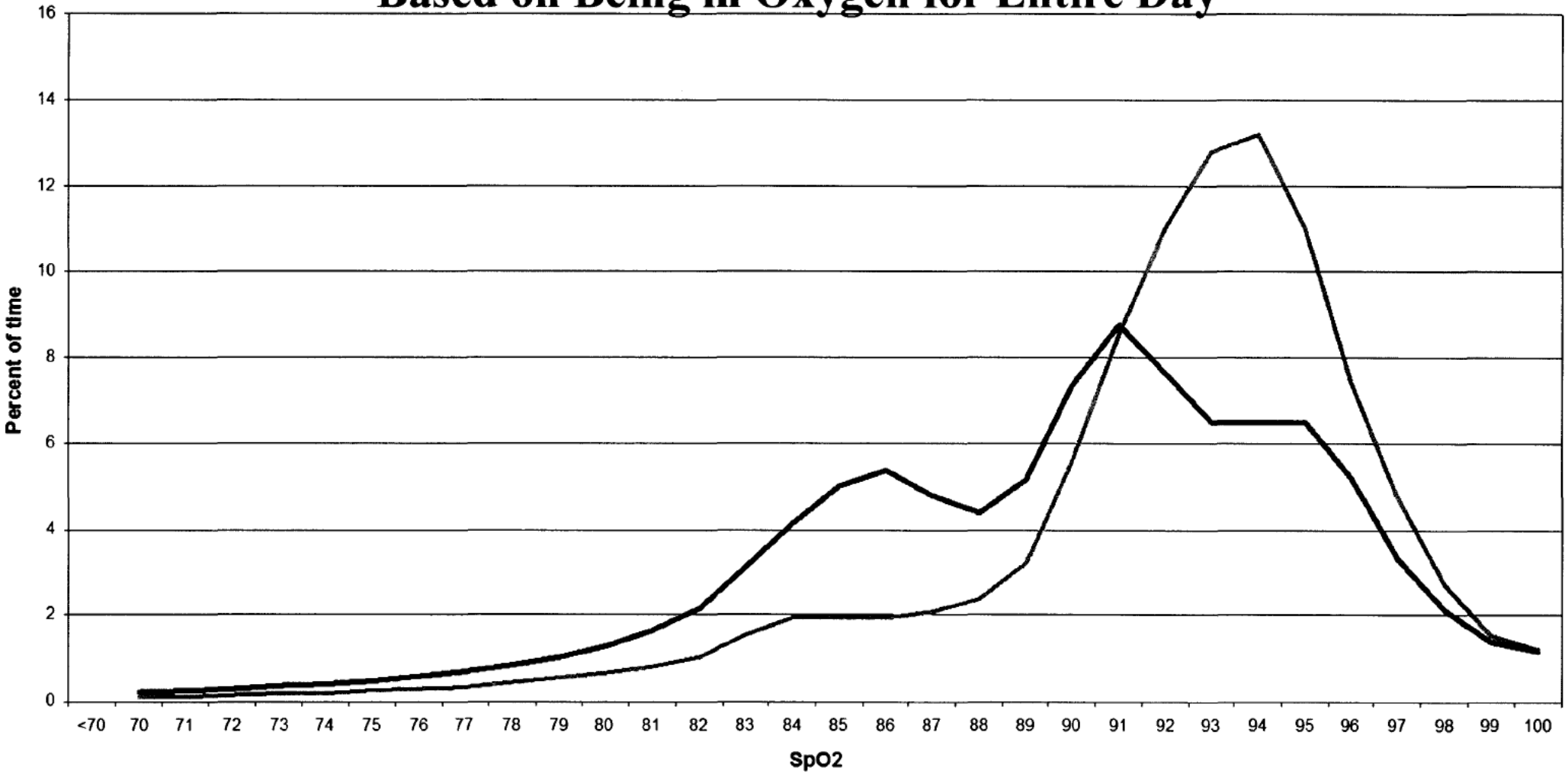
- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% based on all currently available information and the actual SUPPORT Trial Data analyzed to date.**
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 22.9%, 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)**

Percent of time at each SpO2 value (smoothed data)

Based on Being in Oxygen for Entire Day



Slide 23

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% for the 91%-95% group compared to 35.5% for the 85%-89% group.**
- **These differences persisted for data beyond 14 days**

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 for the first 14 days of life**

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: Petrie, Carolyn
To: Poole, W. Kenneth; 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: Zaterka-Baxter, Kristin; Petrie, Carolyn
Subject: SUPPORT--Ancillary: Protocol
Date: Tuesday, January 10, 2006 10:54:43 AM

Please send your availability to discuss the proposed SUPPORT Ancillary "The effects of oxidative stress on the neonatal alveolar macrophage" on these following dates (please include time zone):

Wed, Jan 25
Fri, Jan 27
Mon, Jan 30
Tues Jan 31

Hello Everyone
Please have a look at this new SUPPORT ancillary. I doubt that we will get
to it at our meeting, but we will try to briefly discuss and then set up a
conference call.
See you on Thursday
Safe travels.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 10, 2006 4:14 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT--Ancillary: Protocol

Hi neil,
Would you like us to distribute this to the subcommittee? We could set up a
call following the steering committee meeting, perhaps within a day or 2 of
the dsmc meeting? Let me know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Barbara Stoll <barbara.stoll@oz.ped.emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; petrie@rti.org <petrie@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Jan 09 23:51:31 2006
Subject: SUPPORT--Ancillary: Protocol

<<Protocol 1.09.06.doc>>

Neil and Rose

I reviewed Neil's slides and hope that the DSMC agrees that this trial will
generate important patient care data and that we will be able to put in place additional measures to ensure separation of the groups and limit further the time at very high sat levels.

Obviously dependent on the trial starting again--
Attached is revised ancillary study for SUPPORT Trial-- with budget

Regards

BJS

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"
Subject: FW: SUPPORT--Ancillary: Protocol
Date: Tuesday, January 10, 2006 10:17:12 AM
Attachments: Protocol 1.09.06.doc

Hello Everyone
Please have a look at this new SUPPORT ancillary. I doubt that we will get to it at our meeting, but we will try to briefly discuss and then set up a conference call.
See you on Thursday
Safe travels.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 10, 2006 4:14 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT--Ancillary: Protocol

Hi neil,
Would you like us to distribute this to the subcommittee? We could set up a call following the steering committee meeting, perhaps within a day or 2 of the dsmc meeting? Let me know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Barbara Stoll <barbara.stoll@oz.ped.emory.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; petrie@rti.org <petrie@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Mon Jan 09 23:51:31 2006
Subject: SUPPORT--Ancillary: Protocol

<<Protocol 1.09.06.doc>>

Neil and Rose

I reviewed Neil's slides and hope that the DSMC agrees that this trial will generate important patient care data and that we will be able to put in place additional measures to ensure separation of the groups and limit further the time at very high sat levels.

Obviously dependent on the trial starting again--
Attached is revised ancillary study for SUPPORT Trial-- with budget

Regards

BJS

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

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January 7, 2006

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 SUPPORT trial. Since the analyses focus on the relationship between oxidant stress markers and alveolar macrophage maturation, samples obtained from each intubated SUPPORT baby would be compared to itself across time. With the exception of sample collection, there is no intervention to the enrolled SUPPORT patient.

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

Patient Population: Tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage analysis from participating NICHD NICUs. Locally at the Emory University NICUs, tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage functional analysis and fluid analysis from the two participating SUPPORT 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. Parental consent will be obtained for this Ancillary Study at the time of SUPPORT enrollement. Because this study involves only sample collection (tracheal aspirates) an addendum to the current SUPPORT parental consent will be required, or alternatively, obtaining IRB approval from the center for verbal consent only (as at Emory University for similar studies in the past) could be obtained.

Inclusion criteria: All newborns admitted to the NICU with gestational age of 24 0/7-27 6/7 weeks eligible and enrolled in the SUPORRT Trial 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. 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 written or verbal informed consent (Emory Univ IRB has approved verbal consent for similar studies in the past, Gauthier #388.99), the TA will be obtained at the time of routine endotracheal suctioning as outlined below in Table 1:

Table 1

Begin Enrollment	Sample 1	Birth < 24 hr age
	Sample 2	Day 1 of life
	Sample 3	Day 2 of life
	Sample 4	Day 3 of life
	Sample 5	Day 7 of life
	Sample 6-8	Day 14, 21, 28 of life respectively
End Study		

SUPPORT patients randomized and maintained on CPAP will not have sample collection. Patient sample collection will end when the patient is extubated from the ventilator or at 28 days of life if still intubated. If the enrolled baby is extubated prior to 28 days of life and then reintubated, sample collection will resume at the schedule described above until the endpoint of 28 days of life.

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 provided labeled test tube containing fixative media and labeled with the study number. These samples may be collected by the bedside nurse or respiratory therapist and then saved for the research nurse. The labeled samples will need to be stored in the refrigerator, bundled and then shipped from outlying centers on dry ice to the Neonatology Laboratory of Emory University, Atlanta, GA for analysis. For samples collected locally in Atlanta, the labeled sample will be transferred to a tube containing only nutrient media and 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 2** below. Macrophage apoptosis will be measured by fluorescent cleavage of poly (ADP-ribose) polymerase (PARP), an early indicator of the apoptosis pathway (38).

Table 2 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 for SUPPORT enrollment is ~67% of eligible infants.

6. Available population/compatibility with other ongoing protocols. Locally at the Emory University NICUs, tracheal aspirate samples from intubated SUPPORT patients will be obtained for alveolar macrophage analysis and fluid analysis from two hospitals (Crawford Long Hospital and Grady Hospital are both enrolling patients in the Support trial) 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 in SUPPORT enrolled patients 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 from intubated patients in the SUPPORT trial to obtain statistical significance in the macrophage analysis as described above. This assumes that more sites than Emory will participate. Enrollment from the entire network would increase enrollment from approximately 2 intubated patients per month enrolled in SUPPORT at Emory to approximately 10-15 patients per month. If all sites participate, study will be completed in less than 1 year.

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 of intubated SUPPORT patients, when used only for clinical indications, as per individual NICU routine. Therefore, there are no other risks to the patient from this ancillary study. There are no direct benefits for the individual subjects to participate in this proposal.

I. Budget: In order to achieve statistical significance, the budget assumes a sample size of 47 patients with 8 samples/patient for a total of 376 samples and duration of 1 year.

Nursing Budget:

~ 5 hours per patient x 47 patients = 235 hours

235 @ $32/hour = $7520 + 25% fringe ($1,880) **$ 9,400**

Laboratory Budget:

Salaries: Research Technician (Levan Gabelaie) **$ 9,500**

25% effort for 1 year (including fringe) for alveolar macrophage isolation, immuno staining and confocal immunohistochemical analysis.

Supplies:

Sample Tube Preparation	**$ 500**
Primary Antibodies for cell markers and apoptosis, Fluorescent Secondary Antibodies Fluorescent Bacteria, nutrient media	**$ 7,500**
	Total: $26,900

J. References Sited

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From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT--Ancillary: Protocol
Date: Tuesday, January 10, 2006 10:14:40 AM

Hi Rose
I agree with your thoughts. Let's circulate to the subcommittee and we can discuss by phone
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 10, 2006 4:14 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT--Ancillary: Protocol

Hi neil,
Would you like us to distribute this to the subcommittee? We could set up a call following the steering committee meeting, perhaps within a day or 2 of the dsmc meeting? Let me know.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

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From: Barbara Stoll <barbara.stoll@oz.ped.emory.edu>
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Neil and Rose

I reviewed Neil's slides and hope that the DSMC agrees that this trial will generate important patient care data and that we will be able to put in place additional measures to ensure separation of the groups and limit further the time at very high sat levels.

Obviously dependent on the trial starting again--
Attached is revised ancillary study for SUPPORT Trial-- with budget

Regards

BJS

From: Duara, Shahnaz
To: adas@rti.org; wcarlo@peds.uab.edu; edward.donovan@cchmc.org; poo@rti.org; nfiner@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh
Subject: SUPPORT Trial Final DSMC Response - Jan 9.ppt
Date: Monday, January 09, 2006 6:21:34 PM
Attachments: SUPPORT Trial Final DSMC Response - Jan 9.ppt

Hi Neil;

I looked over the presentation - thanks for the hard work! The only slide that is not completely clear to me is Slide 16. I assume you will explain it carefully but the numbers could be confusing. Otherwise my comments are on the slides.

Shahnaz
<<SUPPORT Trial Final DSMC Response - Jan 9.ppt>>

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 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

- **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.)**

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- **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)**
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- **Sun et al compared units with upper limits of >95% with those of ≤ 95% (Ped Res 2002, 51:350A)**

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  (Anderson Ped Res 2002;51:367A)
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- **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)**
- ✓ **There were 14 centers from 3 countries who provided patient data**
- ✓ **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%**

Response to DSMC

Safety Issue of SpO2>95%

- ✓ **Median SpO2 from Hagadorn study = 95%**
- ✓ **Medians from SUPPORT Oximeter groups – 92% and 94% overall, and 91% vs 93% only for infants 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

d2

SpO2 values of trial infants in Room Air

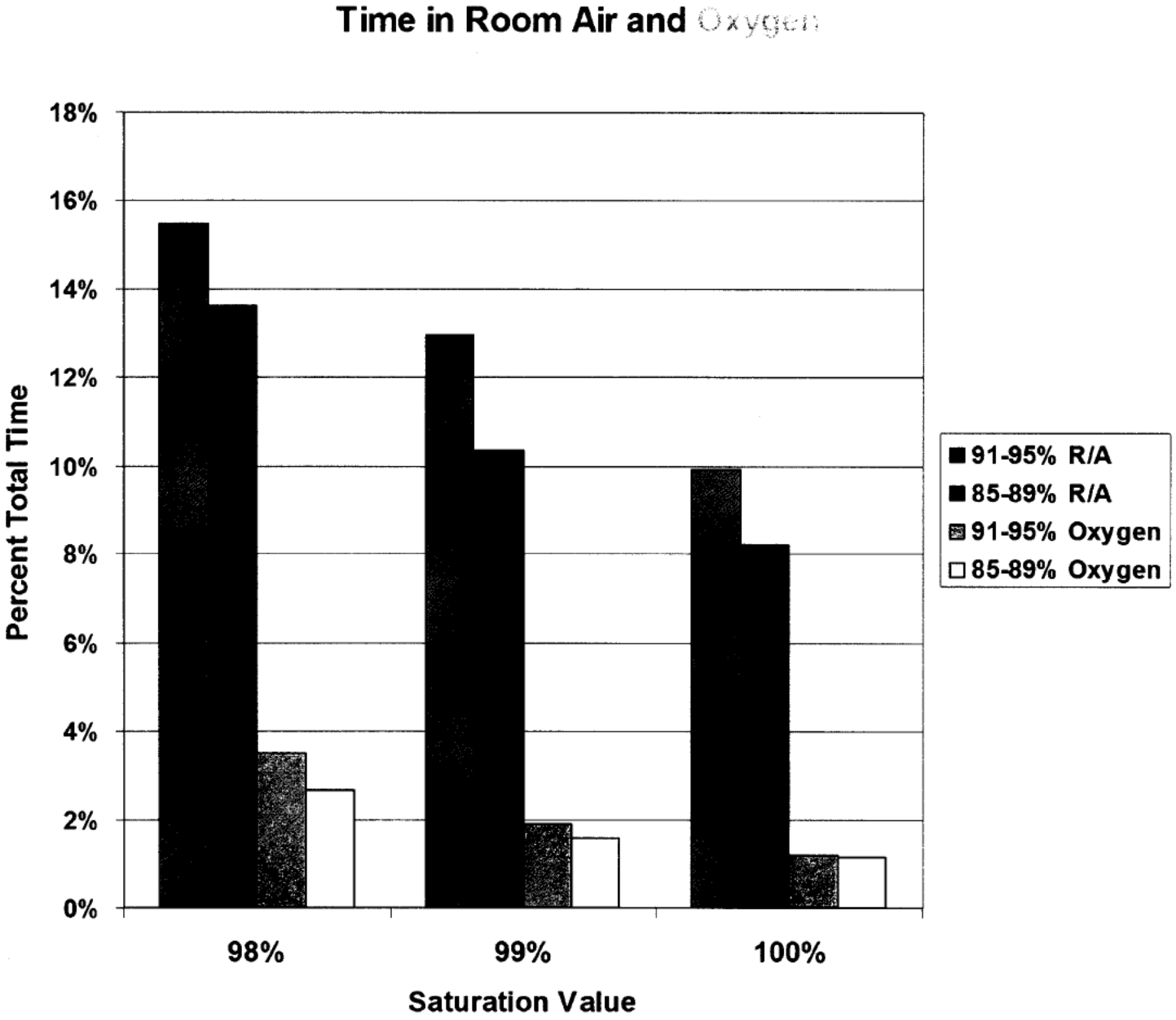
- **Infants in room air had approximately a *six fold* increase in the higher SpO2 durations** d1
- **For SpO2 values > 97%, the cumulative values are shown below and the increased durations at high SpO2s appears equivalent for the 2 target ranges:**

	91%- 95%	85% - 89%
Room Air	**38.3%**	**32.2%**
Oxygen	**6.6%**	**5.4%**

Slide 11

d1 This sentence is not clear - 6 fold over what?
Div of Neonatology, 1/9/2006

d2 Changed the title around - not sure we can say values are the effect of RA; rather, these are values that babies without sig lung disease may attain in RA
Div of Neonatology, 1/9/2006



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 study oximeters display and save values which are altered for SpO2 readings of > 84% to < 96%
- These values which are part of each infants data set are transmitted to RTI as a part of the study.
- This data can be analyzed without applying any correction for the altered values, and this is done to provide feedback to the sites regarding the % of time in range.

Response to DSMC: Safety Issue of SpO2>95%

- To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.
- The design of the algorithm used in the study results in an SpO2 of 88% to 92% being displayed when the actual SpO2 is 91% to 95%
- As a result, when the actual SpO2 increases above 95%, the study oximeter will rapidly change from 93% to 96% or greater

d3

Slide 14

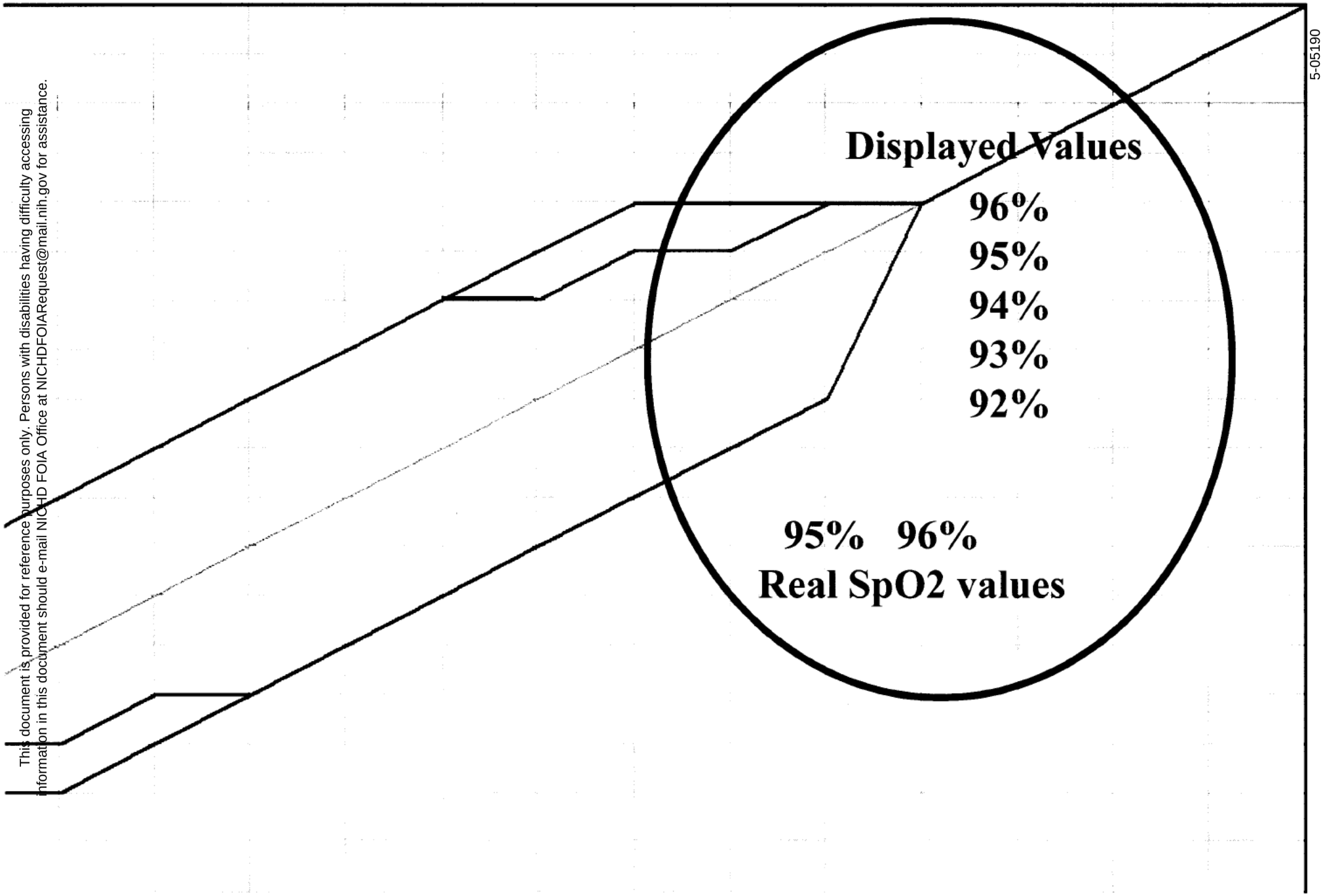
d3

or 85-89%

Div of Neonatology, 1/9/2006

Response to DSMC: Safety Issue of SpO2>95%

- 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



5-05190

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- **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%

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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%

- **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)

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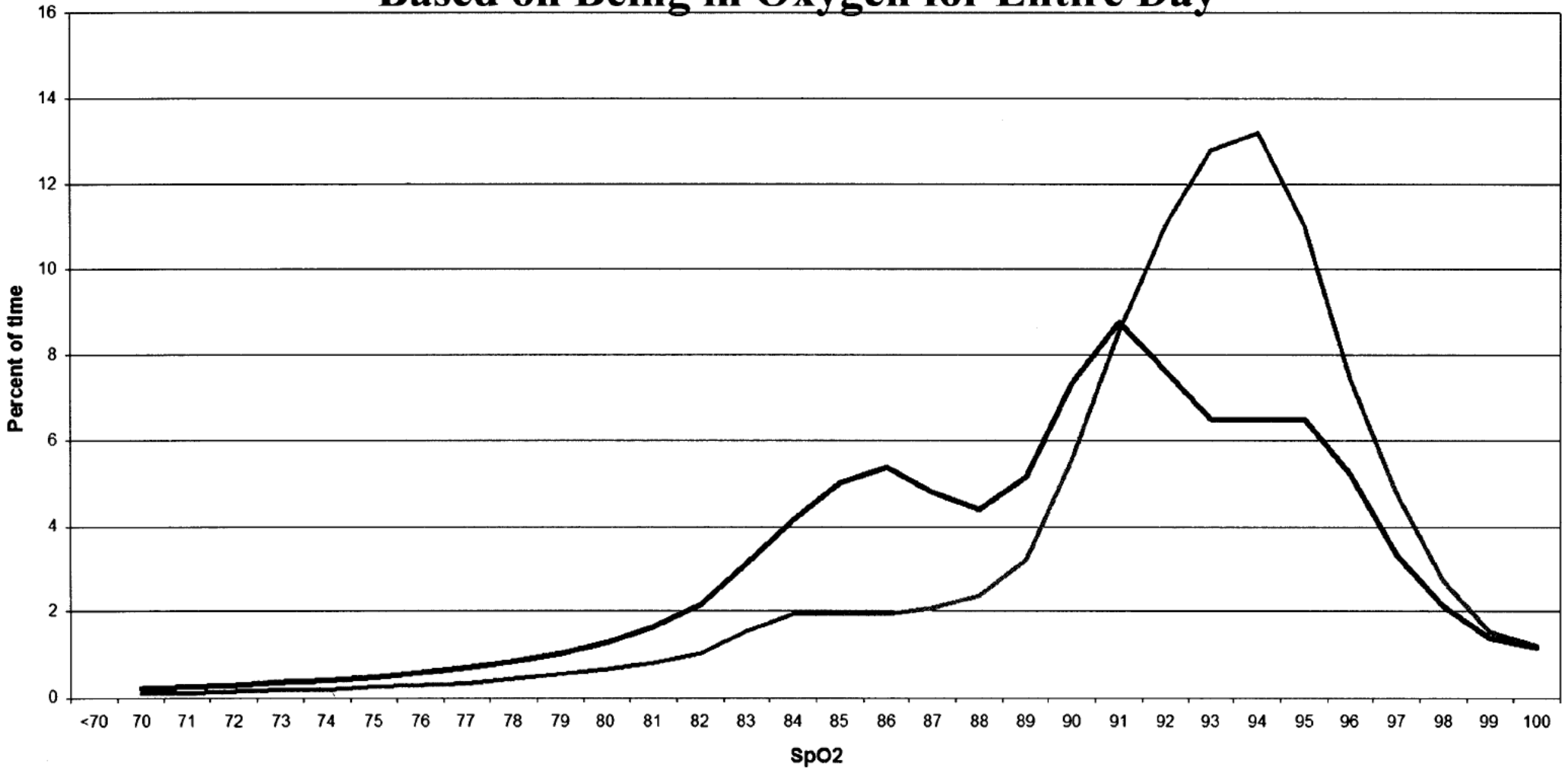
- **Current analyses demonstrate that the highest duration of SpO2 > 95% was 22.9%, and > 96% was 12.5% using only infants known to be in oxygen for all 3 daily data points in the first 14 days of life.**
- **These values are previously unreported for such a population, and significantly less than the 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)**

Percent of time at each SpO2 value (smoothed data)

Based on Being in Oxygen for Entire Day



Slide 23

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Pediatrics, 12/16/2005

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- **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:
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- **The time spent in Room Air during the first 14 days of life was 26.6% for the 91%-95% group compared to 35.5% for the 85%-89% group.** d4
- **These differences persisted for data beyond 14 days**

d4

may be clearer?

Response to DSMC:
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- **The time in 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% 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%**
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7. Initiate compliance monitoring visits coordinated by RTI to visit random sites
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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]; Dale_Phelps@URMC.Rochester.edu
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:	RE: SUPPORT response comments
Date:	Monday, January 09, 2006 1:48:18 PM
Attachments:	SUPPORT Trial Final DSMC Response - Jan 9.ppt Dales comments for Response to DSMC Jan 9 06.doc

Hi Dale
Thanks for the detailed analysis. We have made a number of changes as per your suggestions, and had also designed another graph.
I am enclosing the newer version. Please be as critical at the Steering Comm SUPPORT meeting. We only have 20 minutes to present to the DSMC.
Many thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, January 09, 2006 7:52 AM
To: nfiner@ucsd.edu
Subject: Fw: SUPPORT response comments

Neil
Please look at these suggestions from Dale.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>
Sent: Sun Jan 08 21:45:48 2006
Subject: RE: SUPPORT response comments

<<Response to DSMC.doc>>

Hi Rose,
my comments, will try to send to neil in the am when I get to my desk.
Dale

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
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); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Betty Hastings
Sent: 1/5/2006 8:00 AM
Subject: SUPPORT

HI,

Attached is a PowerPoint presentation which Dr. Finer has prepared for the DSMC open meeting which will be held on January 24 in Rockville. He will present this in brief at the steering committee meeting. If you have comments, please send them.

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>

<<SUPPORT Trial Final DSMC Response - Jan 3.ppt>>

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 9 2005

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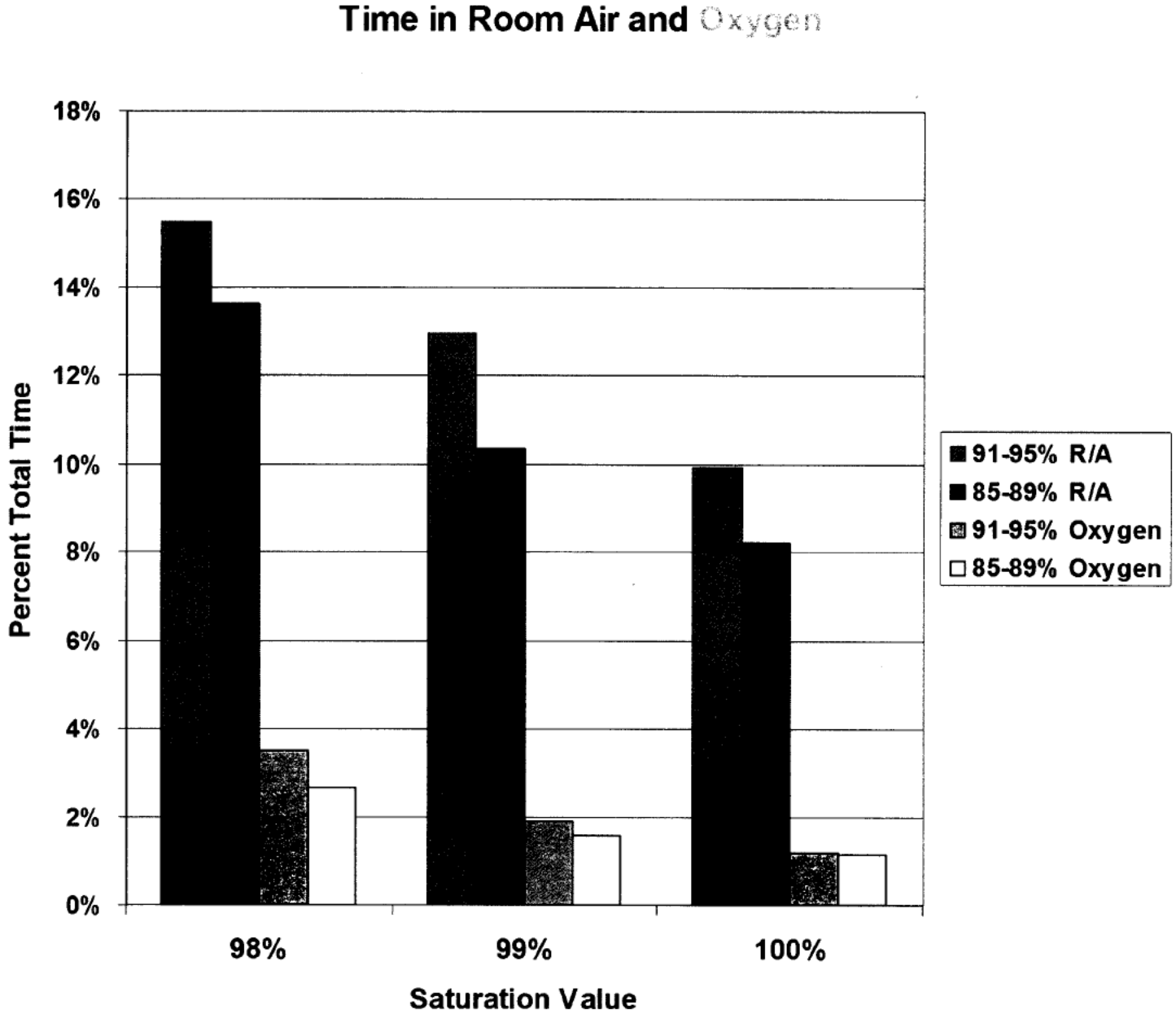

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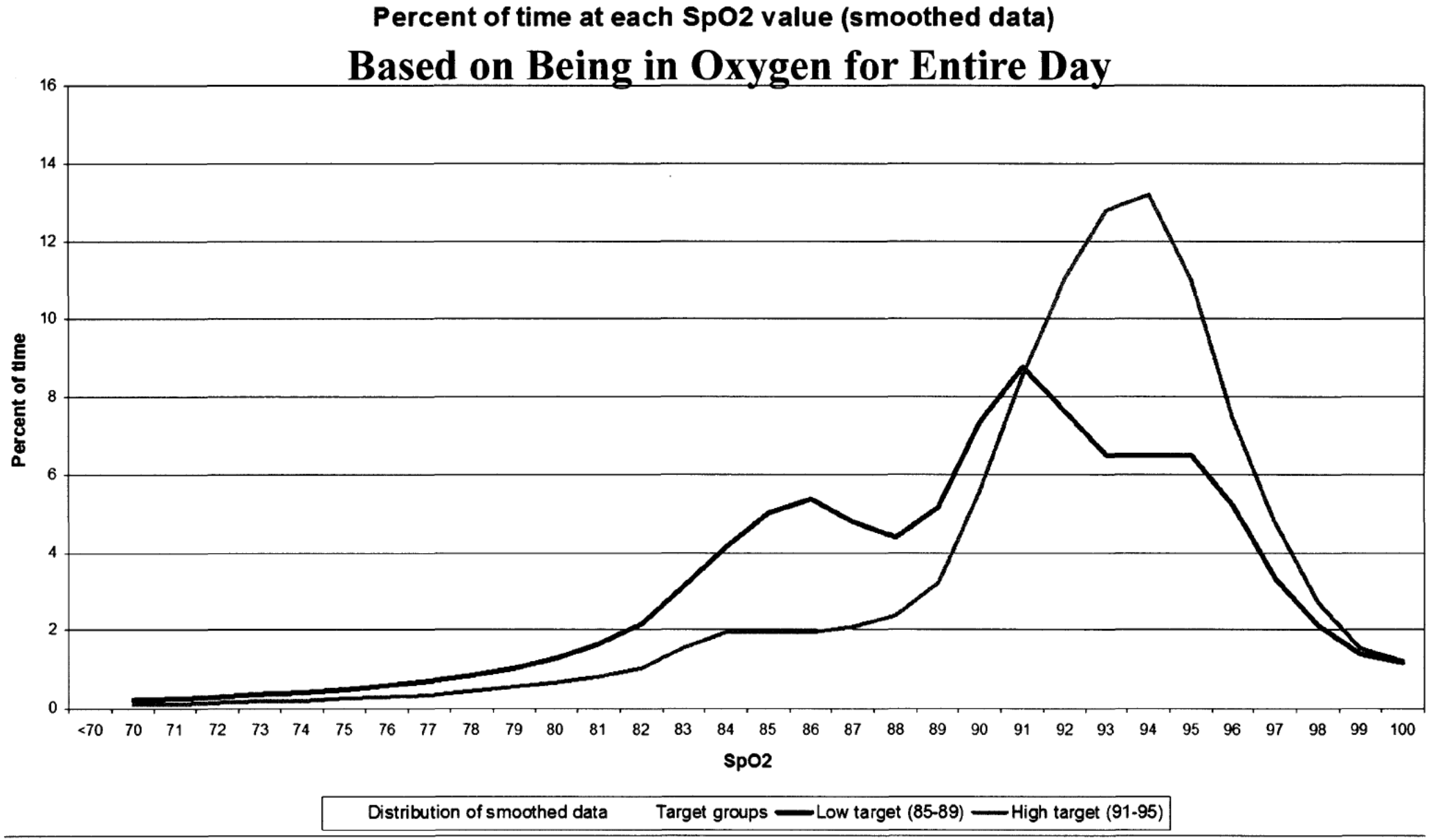

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- **We trust that our response and suggestions to improve the SUPPORT Trial are found acceptable and that we may be allowed to continue this important trial.**

Response to DSMC

Overall, it is hard to know just how this will play out. Given that many on the DSMC are not neonatologists, the seemingly rapid-fire peppering of facts and data may be hard to grasp and keep in perspective. Of course, just looking at the slides always is hard because the spoken word between the bullet points will probably expand and explain things very nicely. It is a complex bunch of things to try and grasp!
Agreed!!

Some specifics:
Silde #6: in the context of the slides up to that point, STOP-ROP has not been brought in, and you've been dealing with early exposure while STOP-ROP is late exposure. Pausing long enough to explain that difference may disrupt the flow of making the points you want. I think I would drop the STOP-ROP line from the context of the series saying that "higher saturations are safe." (you might use is later to show that separation is possible).
Dale – you might have an earlier version – we do not discuss STOP-ROP till slide 10 and then only for 1 line

Slide #11 I find the cumulative % confusing to figure out. By the time I figured out how 12% +15% +9% = 100%, I think I was missing the point of the slide. It would be fine without the cumulative numbers.
We agree and have developed 2 new simpler slides, one of which is a graph. Please let me know if this comes across better.

The next two slides on the saturation algorithms and assumptions and changes in the analyses have to be read very slowly and carefully to grasp, even by me and I think I've had the time to figure this out... so if you fly through this quickly the DSMC may 'give up'. Help them work through what it really means.

Considering switching order of slides 16 and 17 so that the issue of safety is wrapped up before moving on to the futility question.
This was a problem with labeling the slide and we have fixed this

slide #31 "separated by at least 3% duration..." does not make sense. Do you mean separated by at least 3% median saturations? or by 3 days duration of oxygen administration? We have removed this bullet as it remains confusing

The new graph is more encouraging than the first one. Whew! I was about to agree about futility with the DSMC.
However, even more powerful is the effect that kids in the lower sat group are actually receiving oxygen fewer days !!!!! That is a powerful bottom line.
In addition one group is spending almost ¼ of the day more time with lower SpO2s

Just to also consider an alternate viewpoint: If we exclude from the futility monitoring lots of kids who have reached room air, we may be fooling ourselves a

bit. The distributions of ALL enrollees may still be totally overlapping and therefore we might not see a separation when we look at all kids? We certainly will include in all kids in the outcomes analyses, not just the ones receiving oxygen.

We agree but we believe that the study will only be able to alter FiO2 and SpO2 for infants requiring oxygen, and we hope that the overall results demonstrate a difference between the groups. For each child, there is a period of oxygen administration, and that is what we are manipulating.

From: Barbara Stoll
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Attachments: Protocol 1.09.06.doc

Neil and Rose

I reviewed Neil's slides and hope that the DSMC agrees that this trial will generate important patient care data and that we will be able to put in place additional measures to ensure separation of the groups and limit further the time at very high sat levels.

Obviously dependent on the trial starting again--
Attached is revised ancillary study for SUPPORT Trial-- with budget

Regards

BJS

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

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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 SUPPORT trial. Since the analyses focus on the relationship between oxidant stress markers and alveolar macrophage maturation, samples obtained from each intubated SUPPORT baby would be compared to itself across time. With the exception of sample collection, there is no intervention to the enrolled SUPPORT patient.

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

Patient Population: Tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage analysis from participating NICHD NICUs. Locally at the Emory University NICUs, tracheal aspirate samples will be obtained from enrolled intubated SUPPORT patients for alveolar macrophage functional analysis and fluid analysis from the two participating SUPPORT 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. Parental consent will be obtained for this Ancillary Study at the time of SUPPORT enrollement. Because this study involves only sample collection (tracheal aspirates) an addendum to the current SUPPORT parental consent will be required, or alternatively, obtaining IRB approval from the center for verbal consent only (as at Emory University for similar studies in the past) could be obtained.

Inclusion criteria: All newborns admitted to the NICU with gestational age of 24 0/7-27 6/7 weeks eligible and enrolled in the SUPORRT Trial 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. 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 written or verbal informed consent (Emory Univ IRB has approved verbal consent for similar studies in the past, Gauthier #388.99), the TA will be obtained at the time of routine endotracheal suctioning as outlined below in Table 1:

Table 1

Begin Enrollment	Sample 1	Birth < 24 hr age
	Sample 2	Day 1 of life
	Sample 3	Day 2 of life
	Sample 4	Day 3 of life
	Sample 5	Day 7 of life
	Sample 6-8	Day 14, 21, 28 of life respectively
End Study		

SUPPORT patients randomized and maintained on CPAP will not have sample collection. Patient sample collection will end when the patient is extubated from the ventilator or at 28 days of life if still intubated. If the enrolled baby is extubated prior to 28 days of life and then reintubated, sample collection will resume at the schedule described above until the endpoint of 28 days of life.

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 provided labeled test tube containing fixative media and labeled with the study number. These samples may be collected by the bedside nurse or respiratory therapist and then saved for the research nurse. The labeled samples will need to be stored in the refrigerator, bundled and then shipped from outlying centers on dry ice to the Neonatology Laboratory of Emory University, Atlanta, GA for analysis. For samples collected locally in Atlanta, the labeled sample will be transferred to a tube containing only nutrient media and 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 2** below. Macrophage apoptosis will be measured by fluorescent cleavage of poly (ADP-ribose) polymerase (PARP), an early indicator of the apoptosis pathway (38).

Table 2 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 for SUPPORT enrollment is ~67% of eligible infants.

6. Available population/compatibility with other ongoing protocols. Locally at the Emory University NICUs, tracheal aspirate samples from intubated SUPPORT patients will be obtained for alveolar macrophage analysis and fluid analysis from two hospitals (Crawford Long Hospital and Grady Hospital are both enrolling patients in the Support trial) 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 in SUPPORT enrolled patients 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 from intubated patients in the SUPPORT trial to obtain statistical significance in the macrophage analysis as described above. This assumes that more sites than Emory will participate. Enrollment from the entire network would increase enrollment from approximately 2 intubated patients per month enrolled in SUPPORT at Emory to approximately 10-15 patients per month. If all sites participate, study will be completed in less than 1 year.

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 of intubated SUPPORT patients, when used only for clinical indications, as per individual NICU routine. Therefore, there are no other risks to the patient from this ancillary study. There are no direct benefits for the individual subjects to participate in this proposal.

I. Budget: In order to achieve statistical significance, the budget assumes a sample size of 47 patients with 8 samples/patient for a total of 376 samples and duration of 1 year.

Nursing Budget:

~ 5 hours per patient x 47 patients = 235 hours
235 @ $32/hour = $7520 + 25% fringe ($1,880) **$ 9,400**

Laboratory Budget:

Salaries: Research Technician (Levan Gabelaie) **$ 9,500**
25% effort for 1 year (including fringe) for alveolar macrophage isolation, immuno staining and confocal immunohistochemical analysis.

Supplies:

Sample Tube Preparation	**$ 500**
Primary Antibodies for cell markers and apoptosis, Fluorescent Secondary Antibodies Fluorescent Bacteria, nutrient media	**$ 7,500**
	Total: $26,900

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Attachments:	SUPPORT Trial Final DSMC Response - Jan 9.ppt

Hi Neil;

I looked over the presentation - thanks for the hard work! The only slide that is not completely clear to me is Slide 16. I assume you will explain it carefully but the numbers could be confusing. Otherwise my comments are on the slides.

Shahnaz
<<SUPPORT Trial Final DSMC Response - Jan 9.ppt>>

SUPPORT Trial
Response to the DSMC

Neil Finer – Principal Investigator

For the SUPPORT Subcommittee and the Steering Committee

NICHD Neonatal Research Network

Jan 13, 2006

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."

Summary of Responses

- **There is a paucity of information regarding the usual or ideal durations of SpO2 above 95% for ELBW Infants**
- **Infants in RA have significantly greater durations of SpO2 values > 95% than infants receiving Oxygen.**
- **Once we corrected for the effect of room air, the durations of SpO2 > 95% became significantly shorter**

Summary of Responses

- **Study groups do show a difference for saturation exposures.**
- **The oximeter groups differ by > 9% in their durations in room air with the *85%-89% Group spending more time in Room Air.***
- **We can do better and will present plans to improve both separation and reduce durations of elevated SpO2s**

Evidence for Currently used SpO2 Ranges is Lacking

- The optimal saturation range for ELBW is not currently known.
- The Oximeter Arm of the SUPPORT Trial was designed to create 2 groups of ELBW infants who were managed at different SpO2 ranges and had different exposures to oxygen.

Evidence for Currently used SpO2 Ranges is Lacking

- **SUPPORT Trial alarm limits were chosen as those most currently utilized within the Network and consistent with current evidence.**
- **Prior to the initiation of this study not all centers always used a high SpO2 alarm.**
- **Published studies of oxygen administration in older ELBW reported saturation target ranges for populations but did not present data on adherence to targets.**

Published Evidence

- **Sun et al compared units with upper limits of >95% with those of ≤ 95%**
  - (Ped Res 2002, 51:350A)
- **Tin et al reported units by the limits they set without any individual patient data.**
  - Arch Dis Child 2001;84:f106)

Published Evidence

- **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 practice changes including lowering the SpO2 limit – Did not provide actual data**

  -Chow et al, Pediatr 2003;111:339

- ***All of these observational studies suggested that lower SpO2 limits were associated with less ROP.***

Evidence for Currently used SpO2 Ranges is Lacking But Needed

- **Prior to the initiation of SUPPORT – no available data on the percent of time ELBW infants spend at different SpO2 values**
- **This trial using oximeter downloads is unique and will provide needed saturation information on a large prospective cohort**
- **This trial is also unique in collecting this data in acutely ill unstable ELBW infants from 2 hours of age until they are out of oxygen.**

Current Best Evidence- Hagadorn et al

- **14 centers from 3 countries provided actual oximeter data in 78 ELBW infants for 70 hours/week for first 4 weeks**
- **Study performed to document practice prior to a trial with design parallel to SUPPORT**
- **Reported SpO2 limits ranged:**
  - Lower limit 83% -92%
  - Upper limit 92%-98%

PAS 2004 Abstract: Late Breaker

Current Best Evidence- Hagadorn et al

- **Median SpO2 in Hagadorn = 95%**
- **Median SpO2 from SUPPORT –**
  - All infants in trial = 92% and 94%
  - Infants in Oxygen = 91% and 93%
- **Thus infants in SUPPORT have lower median saturations than those in the only prospectively documented cohort.**

Additional Evidence

- **Current evidence suggests that ELBW infants spend about 50% of the time with SpO2s > 95%**
- **Hagadorn study-**
  50% of the time with SpO2 > 95%
- **STOP-ROP high target infants-**
  97% of time SpO2> 95%
- **Case Western – Concurrent ELBW nonSUPPORT**
  51% time SpO2 > 95%

84% and 96%: switch from altered to all real values

- These points are where altered and real values overlap, by nature of the SUPPORT SpO2 algorithm
- Entirely real SpO2 values in SUPPORT are > 96% and < 84%
- Therefore, subsequent data will be presented for values > 96% and < 84%, rather than the expected >95% and <85%

SpO2 values of SUPPORT infants in Room Air

- **Infants in room air had a > *four fold* increase in the time spent at SpO2 > 96% compared with infants receiving oxygen.**

	91%- 95% Group	85% - 89% Group
Room Air	**52.7%**	**46.1%**
Oxygen	**12.6%**	**9.4%**

Durations of SpO2 > 96% for infants in Room Air and Oxygen - Data from SUPPORT Trial

Impact of the Saturation Algorithm

- **The algorithm for conversion of actual to displayed values results in an inability to create a whole value for each displayed value.**
- **The study oximeters display and save values, which are altered for SpO2 readings of > 84% to < 96%**
- **These stored values are transmitted to RTI.**
- **This data can be analyzed without applying any correction for the altered values, and is done to provide feedback to the sites regarding the % of time in range.**

Impact of Algorithm

- **To keep the investigators blinded, the DSMC was requested to evaluate the true (converted) SpO2 values.**
- **The effect of room air on the durations of higher values of SpO2 was not initially anticipated and only became obvious with subsequent analyses.**

Impact of Algorithm

- **To provide better information and avoid the problem with the re-conversion algorithm, subsequent analyses focus on saturations > 96% and < 84%.**
- **These are values are always unaltered.**

Impact of including infants in oxygen for portion of day

- **Analyses that incorrectly assigned infants on room air to be analyzed as receiving Oxygen would overestimate saturations > 95%**
- **Initial analyses assigned infant to oxygen if given oxygen for any part of day. Our data forms sample 3 FiO2 data points daily for the first 14 days and thereafter a single daily value.**
- **This incorrectly assigned some infants in RA to the Oxygen analysis.**

Initial RTI Analyses

Percent of time of spent at SpO2 < 84% and > 96% for the first 14 days of life (Initial RTI Analyses In Oxygen, Dec 2, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	8.3%	14.1%
> 96%	21.5%	15.5%

Corrected RTI Analyses

Further analyses <u>including only infants on Oxygen at all 3 data points</u> for a given day (first 14 days of life)

(Subsequent RTI Analyses - Dec 5, 2005)

Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.4%	13.3%
> 96%	12.5%	9.4%

Safety Issue of SpO2 > 95%

- **We believe that neither oximeter group in the SUPPORT trial is being exposed to excessive durations of SpO2 > 95% while receiving oxygen.**
- **Previous analyses overstated the exposure.**
- **Most of the overestimate was from misclassification of infants in partial oxygen.**

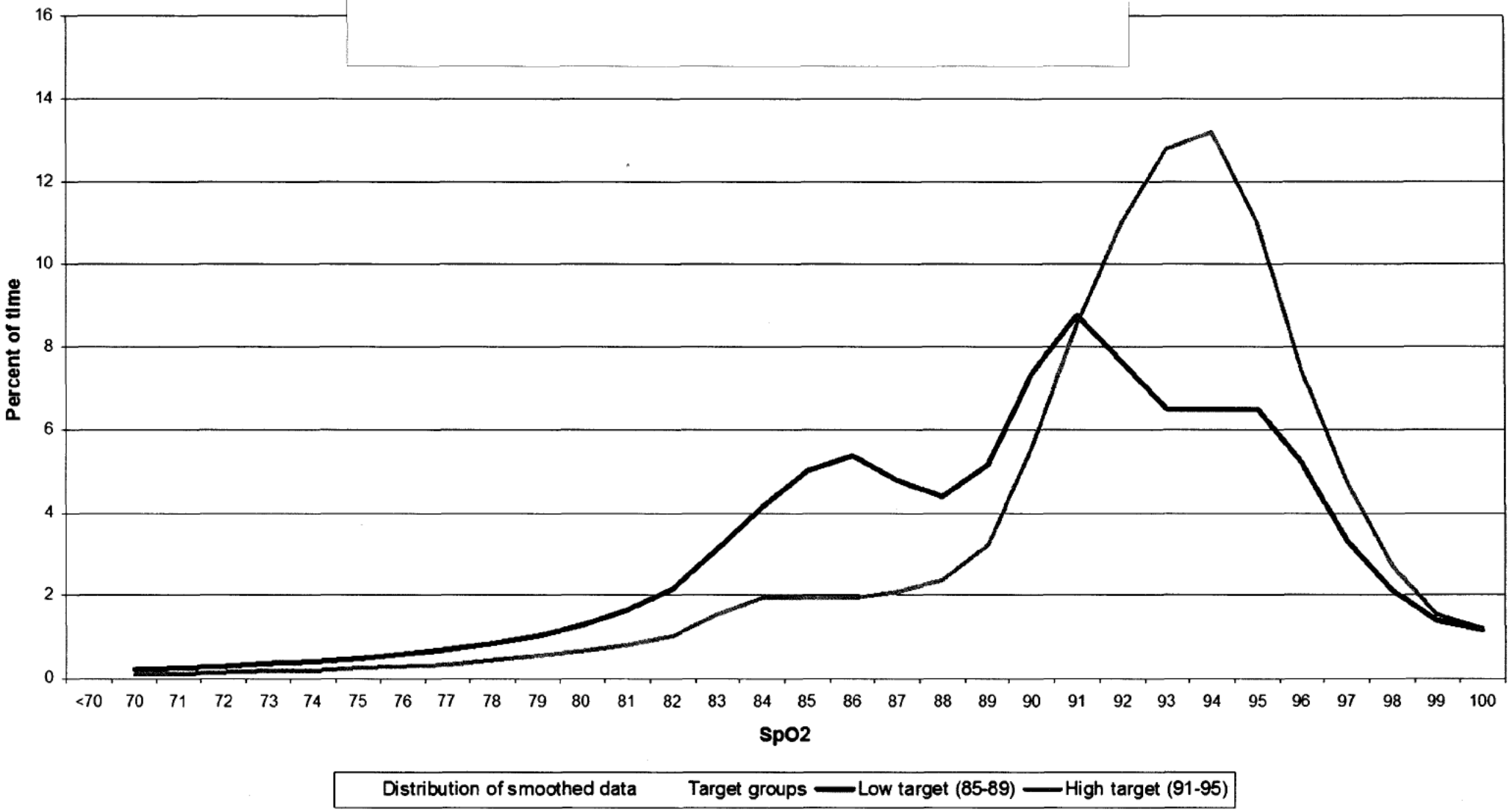
Safety Issue of SpO2 > 95%

- **This trial will help to determine the safe limits of durations of both low and high SpO2 values for ELBW infants by comparing the durations of SpO2 in the 2 groups and their short and long-term outcomes.**

DSMC pt 2: Futility regarding Separation of Oximeter Groups

- **There are saturation value differences for the 2 groups overall.**
  - Mean all infants– 90% vs 92%
  - Median all infants– 92% vs 94%
  - Median infants in oxygen at all 3 data points- 91% vs 93%
- **Time with an SpO2 of ≤90% shows a difference of > 24%**
  - 91% - 95% Group 22.8%
  - 85% - 89% Group 47.6%

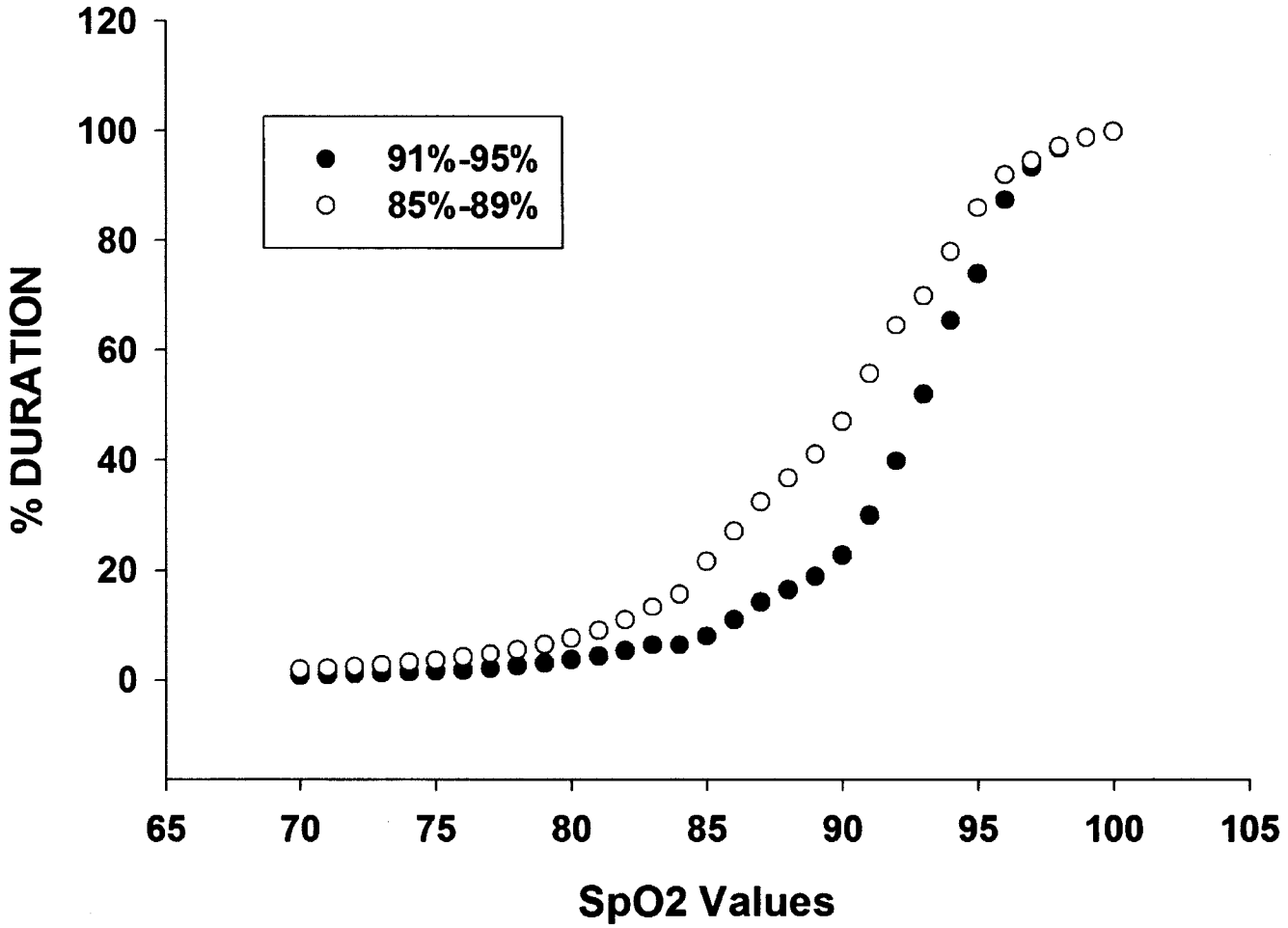
Based on Oxygen Days



Slide 26

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

Smoothed Cumulative SpO2 Durations Based on Oxygen Days



5-05285

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**

Separation of Oximeter Groups

- **Time spent in Room Air during the first 14 days of life was substantially higher in the low target group:**
  - 91%-95% group 26.6%
  - 85%-89% group 35.5%
- **These differences persisted for data beyond 14 days**

Oximeter Groups are Separated

- **It is uncertain what differences in either SpO2 or FiO2 will be associated with different short and long term outcomes.**
- **The randomized groups are separated currently.**
- **We believe that greater separation is desirable and have recommended changes to ensure this.**

Protocol Changes Recommended

1. **Require documentation that the oximeters alarm limits are functional per protocol every 4-6 hours**
2. **Change our data collection for FiO2 to ensure that subsequent interval reports more accurately reflect whether the infant was receiving Oxygen or room air.**

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

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 84% and 96%. We will use the OWL (Oxygen with Love Program) developed at Oschner.
4. Develop guidelines for managing desaturations such that the increase in oxygen is proportional to the desaturation

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

5. Place bedside cards to indicate the desired target range
6. Initiate compliance monitoring visits coordinated by RTI to visit random sites

Suggestions for Increasing Separation of Oximeter Groups, and Decreasing Durations of High SpO2

7. Reanalyze group differences after an additional 100-150 infants have been enrolled.
8. Utilize only actual SpO2 values for assessment of safety in subsequent analyses ie; SpO2 < 84% and > 96%, and analyze only actual time in oxygen.

Conclusion

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

From: Zaterka-Baxter, Kristin
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: DSMC agenda
Date: Friday, January 06, 2006 11:59:45 AM
Attachments: DSMC AGENDA 1 24 06 (2) adrev.doc

Hi,
Abhik made a few changes to the agenda and left the IPGE as tentative. He added a support safety data discussion and said that the DSMC might want an open session at the end to discuss findings but will leave that unsaid for now. He knows you wanted a ½ for Neil to answer any of the DSMC questions but I think Abhik is under the impression Neil will be available the whole day just in case this is the fact. Wanted to let you know the particulars before I sent this out. Still have not heard from Dr. Avery.
Thanks,
Kris

Kristin Zaterka-Baxter, RN, BSN, CCRP
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Telephone: (919) 485-7750
Fax: (919) 485-7762
kzaterka@rti.org

NICHD Neonatal Research Network

Data Safety and Monitoring Committee (DSMC)

Meeting to discuss the protocol for The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants
(The SUPPORT Trial)

The January 24, 2006, meeting of the SUPPORT DSMC will be held at 6110 Executive Boulevard, Suite 902, 9th Floor Conference Room, Rockville, MD. The meeting will start at 8:30 AM and will finish by 3:30 PM. The material to be discussed has been previously sent to the committee. Below is the agenda and participant list for this meeting.

AGENDA

OPEN SESSION

8:30 - 8:40	Introductions	Drs. Higgins and Avery
8:40 - -8:50	Role of the DSMC	Dr. Avery
8:50 - 9:10	Presentation of the SUPPORT Trial	Dr. Finer
9:10 to 9:30	Discussion of Presentation	DSMC, Dr. Finer and Dr. Higgins

CLOSED SESSION

09:30 – 11:00	Presentation of SUPPORT interim monitoring data	Dr. Das and Dr. Gantz
11:00 – 1:30	Discussion and working lunch	DSMC
1:30 – 2:00	Final Discussions and Recommendations for SUPPORT	DSMC
2:00 – 3:30	Discussion of Pilot $IPGE_1$ Study (time permitting)	DSMC
3:30	Meeting Adjourned	

Participants:
Gordon Avery, MD, Chair
Robert Boyle, MD
Carl Hunt, MD
Merran A. Thomson, MD
Christine A. Gleason, MD
Marilee C. Allen, MD
Marian Willinger, Ph.D.
Traci Clemons, Ph.D
Neil Finer, MD (Open Session)
Waldemar A. Carlo, MD (Open Session)
Rosemary Higgins, MD (Open Session)
Mary Ann Berberich, MD (NHLBI) (Open Session)
Abhik Das, Ph.D.
Kenneth Poole, Ph.D. (via phone conference)
Marie Gantz, Ph.D.
Carolyn Petrie Huitema
Kris Zaterka-Baxter (via phone conference)

From: Michele Walsh
To: Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: DSMC presentation for SUPPOT
Date: Friday, January 06, 2006 10:50:59 AM

Neil:
Thanks for working so hard on this!
The delay is really effecting the trial. Our IRB will not process any of the secondary studies (MRI or pulm outcome) until the DSMC resolves this issue!

A few comments on the presentation:
1. Hagadon slide:
Consider expanding. As a late breaker most will not have access to this, and may not have seen it. Also need to explicitly state is observational data from x nmber of NICUs.
2. SUPPORT Trial Results Slide:
Eliminate column with cum% data- confusing and not needed.
3.Safety issue of SpO2>95%
- Discussion of algorithm is complicated but is really at crux of issue for DSMC. I agree with not showing the actual algorithm as it confuses everyone. Suggest the following rewording:
- DAta is only captured on saturation values displayed on the oximeter, not the actual saturation values.
-The algorithm used by RTI to convert displayed saturation values to actual saturation values requires assumptions that lead to all saturation values = 95% being grouped with those >95%.
-This technical requirement leads to an overstatement of time in the hyperoxic range.
- The magnitude of this overstatement in the data previously seen by the DSMC is 6%.
(Hope I have understood the point correctly!)
Michele

From: Zaterka-Baxter, Kristin
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW:
Date: Friday, January 06, 2006 9:35:41 AM
Attachments: DSMC AGENDA 1.24.06.doc

Hi,
I've not heard back from Dr. Avery about the DSMC agenda. I sent the email below on Tues. I'd like to send out the agenda and the logistical memo Monica prepared today so that the DSMC members and RTI have enough time to make travel arrangements and Monica can finalize the hotel contract.
What are your thoughts?
Thanks,
Kris

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kzaterka@rti.org

From: Zaterka-Baxter, Kristin
Sent: Tuesday, January 03, 2006 5:11 PM
To: 'gavery@cnmc.org'
Subject:

Dr. Avery,
Please find attached the tentative agenda for the DSMC Support Study meeting. I've included time to discuss the new inhaled PGE_1 study at the end of the meeting but of course this can be revised as necessary. Your comments/suggestions are appreciated.

Thanks,

Kristin Zaterka-Baxter, RN, BSN, CCRP
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NICHD Neonatal Research Network

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8:50 - 9:10 Open session	Presentation of the SUPPORT Trial	Dr. Finer
9:10 to 9:30 Open session	Discussion of Presentation	DSMC, Dr. Finer and Dr. Higgins
09:30 – 11:00 Closed session	Discussion of Support data and data from other studies	DSMC
11:00 – 11:30 Open session	Question and Answer Session if needed	DSMC, Dr. Finer and Dr. Higgins
11:30 – 1:30 Close session	Working Lunch and Discussion	DSMC
1:30 – 2:00 Closed session	Final Discussions and Recommendations	DSMC
2:00 – 3:30 Closed session	Discussion of Pilot $IPGE_1$ Study (time permitting)	DSMC
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Kenneth Poole, Ph.D. (via phone conference)
Marie Gantz, Ph.D.
Carolyn Petrie Huitema
Kris Zaterka-Baxter (via phone conference)

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD) [E]
Subject:	RE: Network meeting
Date:	Wednesday, January 04, 2006 7:54:57 PM
Attachments:	SUPPORT Trial Final DSMC Response - Jan 3.ppt

Hi Rose
This is the PowerPoint response for the DSMC. I will present to the SUPPORT Subcommittee and then in brief to the Steering Committee. I think it should be circulated to the Steering Committee before our meeting.
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, January 03, 2006 12:32 PM
To: Sood, Beena; Betty_Vohr@brown.edu; Susan Hintz; Kennedy, Kathleen A; Maynard Rasmussen, MD; Brenda Poindexter; Morris, Brenda H; D'Angio, Carl; Guillet, Ronnie; Stevens, Timothy; Michael Cotten; Daniel K Benjamin; alaptook@WIHRI.org; Abhik Das; Carlo Waldemar (E-mail); Charles Rosenfeld; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Jobe Alan (E-mail); Krisa VanMeurs (VanMeurs, Krisa); 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; Zaterka-Baxter, Kristin; Betty Hastings
Subject: Network meeting

Hi,
Please send all materials for the steering committee next week by Monday January 9, 2006.

Thanks
Rose

Rosemary D. Higgins, M.D.
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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

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)

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)

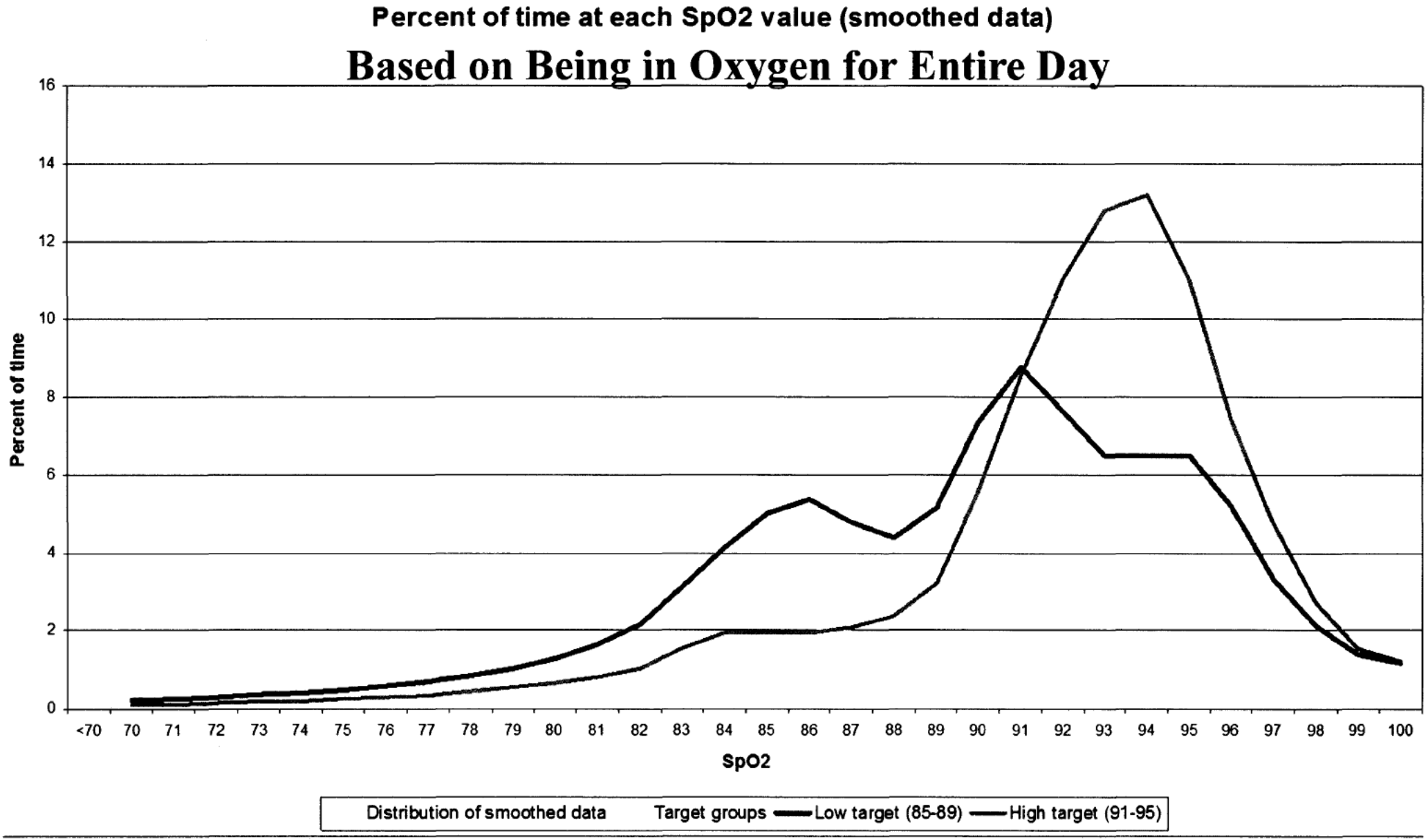
Range Assigned	High target (91-95)	Low target (85-89)
< 84%	6.40%	13.3%
> 96%	12.5%	9.39%

Response to DSMC: Safety Issue of SpO2>95%

- 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)**



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:	Zaterka-Baxter, Kristin
To:	Clemons, Traci (NIH/NICHD)
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Hastings, Betty J.; Petrie, Carolyn
Subject:	NICHD NRN DSMC
Date:	Wednesday, January 04, 2006 1:45:37 PM
Attachments:	Phototherapy Protocol.doc Phototherapy Consent.doc SUPPORT Protocol.doc Support Consent.doc IPGE1 Protocol.doc IPGE1 Consent.doc

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Hello Dr. Clemons and welcome.

Dr. Higgins would like me to send you the protocol and sample consent for three of the NICHD Neonatal Research Network studies that are monitored by the DSMC. The studies are as follows:

1. *A Randomized Trial of Aggressive or Conservative Phototherapy for Extremely Low Birth Weight Infants*

2. *The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The **SUPPORT** Trial)*

3. *Randomized Clinical Trial of Inhaled Pge_1 in Neonatal Hypoxemic Respiratory Failure (study initiation pending final IND approval)*

I would also like to send you additional information regarding the Support trial for the upcoming DSMC meeting which will be held on January 24th in Rockville MD. These materials will be sent by fed-ex so I would also like to confirm your address below:

Traci Clemons, Ph.D.
Statistician
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850

The agenda and additional logistical information for the upcoming DSMC meeting will be sent out shortly. Please don't hesitate to contact me if you have any questions or require assistance in the future.

Thanks,

Kristin Zaterka-Baxter, RN, BSN, CCRP
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National Institute of Child Health and Development

Neonatal Research Network

A Randomized Trial of Aggressive or Conservative Phototherapy for Extremely Low Birth Weight Infants

Subcommittee Members:
Brenda Morris, MD
William Oh, MD
Jon Tyson, MD, MPH
David Stevenson, MD
Dale Phelps, MD
Michael O'Shea, MD
Kenneth Poole, PhD
Linda Wright, MD

August 20, 2002

A. ABSTRACT

Phototherapy has been administered to 94% of ELBW infants who survive more than 12 hours in Network centers. Yet, the serum bilirubin level that is harmful to ELBW infants is unclear and there are no data from large or recent clinical trials to define the risk, benefits, and appropriate indications for phototherapy in these infants. The largest and most recent trial was the NICHD Collaborative Phototherapy Trial which involved infants treated between 1974 and 1976 and included only 77 ELBW infants. Data from this study and others suggest that phototherapy could have important hazards as well as important benefits in ELBW infants.

The proposed study is designed to be a multi-center trial to compare aggressive or conservative phototherapy in ELBW infants. The primary hypothesis is that there will be no difference in death or neurodevelopmental impairment at 18-22 months in infants treated by aggressive or conservative phototherapy regimens. Infants randomized to the Aggressive phototherapy regimen will be started on phototherapy at enrollment (12-36 hours after birth, preferably before 24 hours). In the Aggressive group the infants with birth weight 501-750 mg/dl will have a threshold level for restarting and stopping phototherapy of 5 mg/dl for DOL #1-14. In the Aggressive group for infants with birth weight 751-1000 gms the threshold level for restarting and stopping phototherapy will be 5 mg/dl for DOL #1-7 and 7mg/dl for DOL #8-14. Infants randomized to the Conservative phototherapy regimen will be started on phototherapy when the total serum bilirubin reaches a threshold of ≥8.0 mg/dl for infants with birth weights of 501-750 and ≥10.0 mg/dl for infants with birth weights of 751-1000 g. These threshold levels will remain the restart/stop levels for DOL #1-14. The phototherapy regimens are designed to fall within the range of clinical practice and to assure a sizable difference between groups in serum bilirubin levels and duration of phototherapy. An exchange transfusion will be performed in both groups at ≥13.0 mg/dl for infants with 501-750 g birth weight and at ≥15.0 mg/dl for infants with 751-1000 g birth weight. Based on evidence noted below, the trial would not be expected to increase exchange transfusions in ELBW infants.

The primary outcome will be death or neurodevelopmental impairment at 18-22 months corrected age. Secondary outcomes will include death, abnormal neurodevelopmental outcome, deafness, cerebral palsy, patent ductus arteriosus, and retinopathy of prematurity (outcomes related to bilirubin levels or phototherapy in prior studies).

Based on the current mortality in the generic data base and the follow-up assessments, we estimate that the proportion of infants who die or are impaired at 18-24 months will be at least 60% in the group with the higher proportion of such infants. The study is designed to identify a 7% or greater risk difference between the treatment group with the higher rate and the treatment group with the lower rate (power = 0.80; alpha error=0.05). A sample size of 1,552 total infants whose primary outcome would be evaluated is required. Using conservative estimates, 1,976 total infants would need to

be enrolled to meet this requirement. The proposed trial enrollment will last for two years or until 1,976 infants have been enrolled, whichever occurs later. An additional two years would be needed to complete the follow-up evaluations.

B. STATEMENT OF PROBLEM

The trial described below has been designed to be a relatively simple and inexpensive trial that addresses an important question and that can be conducted without interfering with other Network trials in progress or planned. Indeed, reducing variation in the use of phototherapy within and between Network Centers might help to more precisely determine the effect of other interventions that may be influenced by serum bilirubin levels or phototherapy. The need for the proposed trial is evident from the following:

1. Treatment with phototherapy to reduce serum bilirubin is extremely common among ELBW infants.

In the NICHD Neonatal Network phototherapy was administered to 94% of ELBW infants who survived for at least 12 hours during 1997. (This was the last year that phototherapy data was recorded in the Generic Data Base Report.)

2. There has not been a large or recent randomized trial to establish the value and proper indications for administration of phototherapy in ELBW infants.

The largest and most recent trial was the NICHD Collaborative Phototherapy Trial included only 77 ELBW infants. These infants were treated between 1974 and 1976.[1]

3. In the absence of indications established by proper trials, there is great variation in the indications used in clinical practice for administering phototherapy to ELBW infants.

This is clearly apparent in the Neonatal Network. Among infants whose peak bilirubin level reached no higher than 5 mg/dl, the percentage that received phototherapy in the 14 Network centers in 1997 ranged from 0% (3 centers) to 100% (3 centers). The percentage of all ELBW infants who survived for >12 hours who received no phototherapy irrespective of peak serum bilirubin level ranged from 1-20%. Because the Neonatal Network consists of a limited number of academic centers, the variation between Network centers, albeit substantial, is likely to be much less than among all neonatal units in the U.S.

4. Aggressive use of phototherapy may be needed in ELBW infants because of the potential increased risks of kernicterus, hearing loss, motor deficits, and development delay in this highly vulnerable population.

The current theory on the development of bilirubin encephalopathy is based on the assumption that when the level of serum unconjugated bilirubin exceeds the bilirubin binding capacity of albumin, unbound or free bilirubin is generated which readily crosses the blood brain barrier and produces the neuronal injury that leads to encephalopathic

signs and symptoms.[2,3,4,5] If the infant dies, the brain will exhibit typical pathological features of kernicterus. If the infant survives, the long-term neurologic outcome is poor.

The bilirubin binding capacity of albumin (BBCA) has been directly correlated with increasing maturity and is reduced by a number of risk factors including hypoxia, hypothermia, and acidosis.[6] The use of certain drugs or agents also reduces the BBCA due to competition for bilirubin binding sites of albumin.[7,8,9] These observations are consistent with the clinical documentation of kernicterus and encephalopathy in low birth weight infants with relatively low serum bilirubin levels during the 1960s and 1970s.[10,11,12,13,14,15,16] The clinical reports on low serum bilirubin associated brain injury and inverse correlation of bilirubin binding capacity for albumin and maturity were published in the era when the survival rate of ELBW infants was very low. Thus, the BBCA in current ELBW infants has not been studied but might predispose them to brain damage that could be preventable with aggressive phototherapy.

This concern has prompted the use of phototherapy starting at bilirubin levels of 5 mg/dl or less in ELBW infants.[17] In some nurseries, prophylactic phototherapy is routinely used for all infants with a birth weight <1,500 grams.[17] The strongest evidence supporting such aggressive phototherapy comes from observational studies of large cohorts of preterm infants[18,19,20] identifying a progressively increasing risk of later neurodevelopmental deficits with increasing total serum bilirubin levels. In the study by Van de Bor, et al.[20] the prevalence of handicap at 2 years of age increased progressively with each increase of 2.9mg/dL above a value of 6 mg/dL. However, when these infants were evaluated at 5 years of age there was no significant difference in mean serum bilirubin concentration between the children with and without handicap.[21] An association between serum bilirubin levels >11.8 mg/dl and impairment at 5 years of age in a univariate analysis of ELBW infants without intracranial hemorrhage was recently reported in an abstract.[22] In a recent follow-up study of ELBW infants by Hack et al, [23] deafness at 20 months was associated with a serum bilirubin >10mg/dl in multivariate analysis controlling for multiple potential confounders including intracranial hemorrhage.

Within the Neonatal Research Network, analyses have been conducted to relate peak serum bilirubin to the outcome of ELBW infants born between 1994 and 1999. Those who survived to 14 days (an age when peak serum bilirubin is likely to have occurred) (n=3151) were followed to 18 to 22 months. Peak serum bilirubin was significantly related to the odds of death or neurodevelopmental impairment after adjustment for birth weight, fetal growth status (SGA vs. AGA or LGA), sex, ethnicity, intracranial hemorrhage, and center. The odds ratio for death or neurodevelopmental impairment with each unit increase in serum bilirubin was 1.114 (95% confidence interval =1.079-1.151; p< 0.001) (Oh et al, manuscript in preparation). However, it is not possible to measure and correct for all for potential confounders in observational studies of serum bilirubin (see below), and this association may not indicate a causal relationship. A randomized trial like the one proposed will be necessary to better define the independent effect of serum bilirubin on neurodevelopmental outcome.

5. Conservative use of phototherapy for ELBW infants may be warranted because the serum bilirubin levels that are harmful in ELBW infants may be

substantially higher than generally appreciated and serum bilirubin may be an important, beneficial anti-oxidant.

A. Old studies that have influenced treatment guidelines have very limited relevance to current practice. The initial reports of kernicterus in the late 1940's and 1950's occurred during an era when multiple agents were used that are likely to have increased the risk of kernicterus at a given serum bilirubin value. These agents included benzyl alcohol,[24,25] sulfonamides,[26] high doses of vitamin K,[27] and use of hyperosmolar solutions,[28] particularly high doses of sodium bicarbonate (e.g., 6 meq/kg) administered rapidly (by "IV "push"). Most affected infants had severe hemolytic disease. Moreover, serum bilirubin levels were measured less frequently than now. All of these factors would increase the risk of kernicterus at a specific measured level of serum bilirubin.

The risk of kernicterus at a specific serum bilirubin level may also have been higher then than now because phototherapy was not used at that time. Phototherapy detoxifies bilirubin by conversion to photoisomers.[29, 30] The usual laboratory methods for measuring total plasma bilirubin do not distinguish bilirubin from some photoisomers. At a particular measured serum bilirubin value, phototherapy-treated infants will have a greater proportion of their measured bilirubin as nontoxic photoisomers than do infants who have not received phototherapy.

Concern that even low levels of serum bilirubin may cause brain damage in ELBW infants was raised by reports during the1960s and early 1970s of kernicterus identified at autopsy in very low birth weight infants who had serum bilirubin levels between 4 and 10 mg/dL.[11-16] More recently Turkel and associates examined the clinical course of 32 infants with kernicterus matched with 32 infants without kernicterus on autopsy specimens. They were unable to identify any statistically significant variables between these infants including the peak serum bilirubin levels. In the group with kernicterus, the peak serum bilirubin ranged from 5.3-19.1 mg/dl (Mean 8.3 ± 3) compared to 1.8-13.3 mg/dL (Mean 6.9 ± 3 mg/dL) in the nonkernicteric control group.[31] In a separate publication, Turkel and colleagues found that the "yellow staining" of the brain that prompted a diagnosis of kernicterus in some infants often occurred without the classic histological changes of kernicterus.[32] They concluded that these findings do not indicate true kernicterus and may represent terminal staining of already damaged or dead cells in dying infants.

Whatever it's significance, this yellow nuclear staining virtually disappeared after the early 1970s. [33] In a study of infants autopsied between 1984 and 1993, Watchko and Claasen[34] found no infants with yellow nuclear staining at a serum bilirubin of 11 mg/dL or less. Of the infants who did not have kernicterus the peak serum bilirubin levels were as high as 22.5 mg/dl; 56% of these infants had bilirubin levels greater than 10 mg/dL and greater than the exchange transfusion level in the NICHD Phototherapy Study . Moreover, kernicterus was identified in only 3 infants (4%). One had hydrops fetalis and a peak serum bilirubin of 26 mg/dL. One was born at 25 weeks gestation and had a 5 minute Apgar score <3, RDS, intracranial hemorrhage, intestinal perforation, sepsis, a pH<7.0 for 16 hours before death, and a peak serum bilirubin of 11.3 mg/dL. The third was born at 24 weeks and had RDS, intracranial hemorrhage, a cardiopulmonary arrest, disseminated intravascular coagulation, and a peak serum bilirubin of 18.5 mg/dL.

In a 1982 editorial, Lucey asked the question, "How good are the old studies showing a relationship between plasma bilirubin and later brain damage?" He concluded that, "In the light of our new knowledge they are nearly worthless.... I suggest that we cease pretending to know how to prevent kernicterus or brain damage in low-birth-weight infants and face the fact that this remains an unsolved problem."[29] In 1992, Watchko and Oski stated, "In the final analysis, we do not know the true potential for nonhemolytic hyperbilirubinemia to produce brain damage in the premature newborn in the present era." [35] Unfortunately, this problem is still unresolved.

B. The observational studies prompting aggressive use of phototherapy are biased toward underestimating the serum bilirubin values that cause neurodevelopmental deficits. As a group, ELBW infants with the highest bilirubin levels have a predictably lower birth weight, lower gestational age, and a higher incidence of birth trauma, birth asphyxia, postnatal hypoxia, hypotension, hypoglycemia, hyperglycemia, intracranial hemorrhage, infections, and other disorders. Indeed, almost any factor known to cause handicap is associated with hyperbilirubinemia. Efforts to accurately measure and fully adjust for these confounders are fraught with difficulty. As a result, even the most carefully done and most recent observational studies are likely to identify an association with neurodevelopmental deficits at serum bilirubin levels below those that truly cause neurodevelopmental deficits.

Some observational studies have shown no association between peak serum bilirubin levels and later outcomes. Macgregor and Whitfield evaluated a large cohort of ELBW infants (n=281) and found virtually identical serum bilirubin values among those who were neurologically normal (8.9 mg/dl; range 4.1- 25.3), neurologically equivocal (9.1/dL; range 4.7 –25.3), neurologically abnormal (9.1 mg/dL; range 2.7- 19.9), and the subset of abnormal infants who had sensorineural hearing loss (9.0 mg/dL; range 5.9-12.7).[36, 37] In a cohort study of VLBW infants with serum bilirubin values ranging from 5.8 to 14.6 mg/dL, O'Shea and colleagues found that peak serum bilirubin levels were not associated with neurodevelopmental outcomes when intracranial hemorrhage was included in the multivariate analyses.[38] In the study with the longest reported follow-up in VLBW infants, Van de Bor was unable to show a difference in neurodevelopmental handicap at 5 years of age based on maximal serum bilirubin levels unless there was a significant intracranial hemorrhage.[21] The previously cited study by Hack did not identify an association between serum bilirubin levels >10mg/dL and overall neurological abnormality, developmental delay, or other impairments in ELBW infants.[23]

Such contradictory findings from observational studies cited in Section 4 (above) and here underscore the need for randomized trials to better define the indications for phototherapy and the role of total serum bilirubin.

C. The data from randomized trials, albeit limited, suggests that at least for babies without severe hemolytic disease, the risk of poor neurologic outcomes due to hyperbilirubinemia has been overestimated. In 1965 Wishingrad[39] et al published a randomized trial in which low birth weight infants whose serum indirect bilirubin reached 18 mg/dL were randomized to receive an exchange transfusion. Controls were untreated. Phototherapy--which as noted above is likely to decrease the risk at a given serum bilirubin--was not used at the time this study was performed.

Moreover, serum bilirubin levels were measured only once daily. Ten of 50 control infants had an indirect serum bilirubin greater than 24 mg/dL recorded for more than 48 hours. There were 3 deaths in each group. At 12-24 months, only 6 infants in the control group and 7 in the exchanged group were neurologically abnormal.

In the Collaborative Phototherapy Trial,[40] 1,339 infants were randomized to receive phototherapy for 96 hours or no phototherapy. (The intervention and control groups both received exchange transfusion at the same predetermined level adjusted for BW [Range: 10 mg/dL for ELBW infants to 20 mg/dL for low risk-infants 2000-2500 g BW].) As expected, measured peak and mean serum bilirubin levels were significantly lower among the intervention group than the control group. Follow-up assessments were conducted at 6 years of age. Phototherapy treated infants and controls were almost identical in the proportion with hearing loss (1.8% vs. 1.9%), cerebral palsy (5.8% vs. 5.9%), or clumsiness or hypotonia (11.1% vs11.4%).[41] There was no trend towards higher developmental scores in phototherapy treated infants despite the difference in their mean peak serum bilirubin. Of particular note, no infant in either group developed choreoathetosis, the most distinctive long-term indicator of bilirubin encephalopathy.

6. Conservative use of phototherapy may be needed because phototherapy may be more hazardous than generally appreciated in ELBW infants and moderate levels of bilirubin may be beneficial.

A variety of definite or potential hazards have been identified. These include increased insensible water loss,[42,43] transiently decreased weight gain,[44] and decreased GI transit time,[45,46] shortened platelet half-life,[47] and hemolysis.[48] While these problems are usually not of great clinical importance, there is also evidence that phototherapy increases the incidence of patent ductus arteriosus[49] and retinopathy of prematurity.[40] A worrisome possibility of increased mortality is raised in the largest trial of phototherapy. In the Collaborative Phototherapy Trial[50] (n=1063 low birth weight infants) the relative risk of death among the infants randomized to phototherapy relative to those randomized to no treatment with phototherapy was 1.32 (95% confidence intervals = 0.96-1.82).[51] This finding, albeit not quite statistically significant, is consistent with a 32% overall increase in mortality due to phototherapy and does not rule out an 82% increase. In the subgroup analyses, the relative risk for ELBW infants was 1.49 (0.93-2.94).

It is difficult to conceive of mechanisms by which phototherapy would cause such an increase in mortality. However, there is increasing evidence that phototherapy may have adverse effects. Phototherapy has been reported to cause oxidative injury to the red cell membrane as shown by an increase in the products of lipid peroxidation and hemolysis [52,53] and lysis of platelets.[54] This would increase the oxidative stress and potentially lead to cell and tissue damage. [55,56] Free radical reactions lead to peroxidation of lipids and to DNA damage (fragmentation, apoptosis, base modifications and strand breaks) and therefore have a wide range of potential biologically toxic effects.[57] Oxygen free radicals have been proposed as a contributing factor in the genesis of neonatal diseases such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and patent ductus arteriosus.[58]

Recent evidence is emerging that bilirubin is an important antioxidant in neonates. Dennery and Stevenson demonstrated that significantly less lipid peroxidation was seen in jaundiced Gunn rats compared to non-jaundiced littermates when exposed to high oxygen levels.[59] In premature infants the levels of anti-oxidant enzymes and scavengers are low[60] and bilirubin may be a major contributor to the antioxidant capabilities of the infant.[61] The physiologic elevation of bilirubin in the first week of life may actually be beneficial. This possibility was not recognized when current guidelines for use of phototherapy were developed.

The potential benefits of bilirubin are just beginning to be explored by the pediatric research community. A recent observational study by Yeo, et al.[62] reported an association between an increased incidence of visual loss from retinopathy of prematurity among infants ≤800 g BW and ≤ 27 weeks gestational age and low serum bilirubin levels (<9.4 mg/dL; OR 4.48, CI 1.15-17.43) and long exposure to phototherapy (OR 1.17, 1.02-1.33). This association was observed in a multivariate analyses adjusting for gestational age and duration of phototherapy. The guidelines for initiating and stopping phototherapy in ELBW infants used in this study were, at <36 hours of age, 6.4-9.9 mg/dL; 36-72 hours, 8.5-10.5 mg/dL; 72-120 hours, 10.5-11.7 mg/dL; and >120 hours, 11.1-12.3 mg/dL. The guidelines for exchange transfusion were, at <72 hours, > 11.7 mg/dL and at >72 hours, > 12.6 mg/dL. This study suggests that moderate levels of bilirubin may have important benefits for ELBW infants. Although it was published relatively recently, it has the same methodological limitations as any observational studies relating neurodevelopmental deficits to low serum bilirubin.

C. HYPOTHESIS

The null hypothesis is there will be no difference in the incidence of death or neurodevelopmental impairment between infants exposed to conservative or aggressive phototherapy.

D. SPECIFIC AIMS

PRIMARY OBJECTIVE: To determine whether the incidence of death or neurodevelopmental impairment at 18-22 months among ELBW infants differs according to whether they were treated with aggressive or conservative phototherapy. The study is designed to detect an absolute difference in this outcome of 7% between the groups.

SECONDARY OBJECTIVES:

1. To determine whether the use of aggressive or conservative phototherapy regimen results in differences in mortality before nursery discharge.

2. To determine whether the use of aggressive or conservative phototherapy regimen results in differences at 18-22 months in death, cerebral palsy, Bayley II Developmental scores, blindness, and deafness. Other secondary outcomes include: patent ductus arteriosus requiring drug or surgical treatment, retinopathy of prematurity, chronic lung

disease, ventilator settings and FiO2 at 36 weeks, necrotizing enterocolitis, intracranial hemorrhage (by grade), periventricular leukomalacia, sepsis, and the results of hearing assessments at discharge.

Patent ductus arteriosus and retinopathy of prematurity are included as secondary outcomes because of results of the studies described above noting an association between these outcomes and either phototherapy or serum bilirubin levels. Chronic lung disease and ventilator settings at 6 weeks are included because of the possibility that moderate bilirubin levels might reduce oxidative injury to the lungs. Intracranial hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and sepsis are included as factors that affect the likelihood of death or neurodevelopmental impairment and that require evaluation in assessing whether (and perhaps how) phototherapy affects mortality or neurodevelopmental outcome.

3. To compare the aggressive vs. conservative phototherapy regimens with respect to peak serum bilirubin, age at starting phototherapy, duration of phototherapy, and number of exchange transfusions performed.

4. a) To relate adverse outcomes to various measures of bilirubin exposure (peak total serum bilirubin, peak indirect serum bilirubin, direct serum bilirubin, unbound bilirubin levels (per Dr. Oh's secondary trial), duration of bilirubin values exceeding a particular level) and to assess which measure best predicts adverse outcomes and b) to assess whether these relationships differ by treatment group (phototherapy perhaps affecting the risk of toxicity at a given bilirubin level).

5. To evaluate whether the risk/benefit ratio for aggressive phototherapy is more favorable in association with such factors as sepsis, acidosis, hypoalbuminemia, and hemolytic disease.

6. To determine whether the use of aggressive or conservative phototherapy regimen results in differences at 18-22 months in death or moderate impairment (Bayley MDI or PDI < 85) and to determine if there is a difference between groups for moderate impairment.

E. RATIONALE/JUSTIFICATION

The following issues were important considerations in the design of the proposed trial:

1. What should the primary outcome be? How large a difference between the two treatment groups should the study be designed to detect?

We considered whether the percentage of survivors who have neurodevelopmental impairment should be the primary outcome. However, in an intention-to-treat analysis, all infants randomized including those who died must be included in the primary analysis. Because mortality and severe morbidity are competing

outcomes, we propose the composite outcome of either death or neurodevelopmental impairment at the age of the Network follow-up evaluation. Any positive or negative effect of phototherapy on mortality would be reflected in the primary outcome. If, as clinicians believe, phototherapy has no effect on mortality, the presence or absence of a significant difference between groups in the primary outcome will be entirely dependent on neurodevelopmental outcome.

The proposed sample size was selected to evaluate a 7% reduction in death or impairment (60% vs. 53%) or a relative risk of 0.88 in the group exposed to the treatment regimen found to be better compared to the group who receives the other treatment regimen. The risk difference between groups to be assessed is less than in many neonatal trials. However, a study of this size is required to evaluate whether the "number needed to treat" is 15 infants. That is, whether the superior treatment regimen prevents one additional infant from dying or being impaired for every 15 treated. We project that a difference of this size can be evaluated with at least 80% power by enrolling ELBW infants for 2 years. (See sample size section). If projections from the Neonatal Network from 2001 were used, a power of about 85% would be obtained by enrolling infants for 2 years.

2. To what extent, if any, should the method of administering phototherapy, the wavelength of the light, and the irradiance be regulated by the study protocol?

Phototherapy is provided in a variety of ways throughout the world. Due to concerns that the technique or the intensity phototherapy in the Conservative cohort might be different than the phototherapy given to the Aggressive cohort and that this might influence the outcomes, we have developed guidelines for the use of phototherapy during this trial. The irradiance level for babies on phototherapy should be between 15-40 $\mu W/cm^2/nm$. Phototherapy should be used more aggressively as the baby approaches exchange transfusion criteria. If a baby is within 2mg/dl of an exchange transfusion then phototherapy may be used at the discretion of the attending.

For all infants receiving phototherapy, irradiance will be assessed each weekday by research nurses as a measure of one factor affecting the efficacy of phototherapy. For infants receiving conventional phototherapy, it will be measured at the level of the umbilicus. For infants receiving fiberoptic phototherapy,[63] irradiance will be measured the first day that the baby is on the biliblanket The nurse will also record how many banks of phototherapy lights or biliblankets the baby is receiving. These measurements and recordings should be done at approximately the same time each day.

3. What should be the appropriate bilirubin thresholds for initiating "aggressive" and "conservative" phototherapy regimens? What thresholds should be used for discontinuing phototherapy?

Whatever indications for phototherapy are used, it is important that there should be a substantial difference between groups in the age at initiation, in the total duration of phototherapy, and in mean and peak serum bilirubin values. To produce results relevant to current practice and to facilitate high compliance with the protocol, we also want the conservative and aggressive phototherapy regimen to be within the range used in clinical practice. In addition, the treatment regimens should be relatively simple and not disrupt other aspects of care.

The treatment thresholds selected are shown in the Tables below. Total serum bilirubin rather than indirect bilirubin will be used because indirect serum bilirubin has not been reported in most studies and because direct bilirubin may indirectly contribute to the risk of bilirubin encephalopathy.[17]

In selecting the indications for phototherapy in the aggressive treatment group, we were reluctant to propose prophylactic phototherapy (initiated at or shortly after birth) or to start phototherapy at a time when the mean serum bilirubin was lower than approximately 5 mg/dL, a level below which phototherapy has been found to be ineffective.[64] However, once the serum bilirubin reached this level, we also did not want to delay starting phototherapy because serum bilirubin determinations were not ordered or because of inadvertent delays in reporting the bilirubin value or in ordering or instituting phototherapy. As a result of these problems, phototherapy might be started at a mean serum bilirubin not very different from that of the conservative phototherapy group and the peak serum bilirubin for the two groups might be similar. For this reason, we propose that phototherapy simply be started as soon as feasible between 12 to 36 hours--preferably by 24 hours--in the aggressive phototherapy group. (Up to 36 hours is allowed to facilitate obtaining valid consent from mothers who have difficulty participating in a consent process due to complications of delivery, prior anesthesia, or transfer of the baby.) This decision to obtain consent between 12 and 36 hours was based in part on the findings of Curtis-Cohen, et al.[65] In their study of prophylactic versus routine phototherapy, routine phototherapy was started at a serum bilirubin value of 5mg/dl. Study infants had a mean birth weight of 850±220 g. For infants in the routine phototherapy group, the mean age when the total serum bilirubin was found to reach 5 mg/dL was 27±5 hrs. Thus, we would expect that the mean serum bilirubin at enrollment would be no higher than 5-6 mg/dL in the of the aggressive phototherapy group.

The thresholds for conservative phototherapy (8 mg/dl for ≤750 g infants; 10 mg/dL for 751-1000 g infants) were based on the findings of the observational studies since the 1980s, the two randomized trials discussed above, and current practice in some nurseries. These suggest that the serum bilirubin threshold that causes discernible neurodevelopmental impairment is likely to be no lower than 10 mg/dL and might be considerably higher. (See comments below.)

The findings of the study of Curtis-Cohen should be reassuring to anyone concerned that there would be little or no difference between two treatment groups in mean serum bilirubin. The mean peak serum bilirubin in the routine phototherapy group who received treatment by guidelines similar to those in our aggressive phototherapy group was 7.2 (SD=1.2) mg/dL, a value only 1.2 mg/dL higher than the mean bilirubin at onset of phototherapy (6.0; SD=0.8). This mean peak serum bilirubin is less than the level at which phototherapy would be started in the conservative phototherapy group (8 mg/dL for infants ≤750 g; 10 mg/dL for infants 751-1000 g).

Phototherapy would be used for at least 24 hours whenever it is started or restarted. It would be continued in either group as long as the total serum bilirubin exceeds the threshold values for initiating phototherapy as expressed in **Tables 1 and 2**.

4. Should the bilirubin threshold used as an indication for exchange transfusion be the same for the two treatment groups? What threshold should be used for exchange transfusion?

We propose that the same threshold be used for the two groups so that any difference in outcome of the two groups would be attributable to a difference only in the indication for phototherapy and not a difference in the indication for exchange transfusion.

An exchange level no lower than the one proposed for this trial (13 mg/dL for infants ≤750 g; 15 mg/dL for 751-1000 g infants) is supported by observational studies since the 1980s and by the two randomized trials note above. Indeed, these levels could be considered to be lower than necessary based on the findings of Watchko and Klassen.[34] These authors concluded "...our data suggest that kernicterus is an uncommon event ...and is unlikely to occur even when serum bilirubin levels rise above those previously thought to put the infant at risk. Our data further suggest a less aggressive therapeutic stance ... that would permit serum bilirubin concentrations to approach the 15 to 20 mg/dL range before performing an exchange transfusion." The data of Wishingrad would also support such a conclusion.[39]

If a serum bilirubin level is reached that is higher than the threshold value for exchange transfusion, there are 3 circumstances when the attending neonatologist would have the option to defer an immediate exchange transfusion and to administer intensive phototherapy for up to 8 hours and repeat the serum bilirubin. These 3 circumstances are:

A. The infant has not previously received phototherapy;
B. The phototherapy has been provided in a manner considered to be inadequate by the attending neonatologist.
C. Based on prior serum bilirubin values or clinical findings, the attending neonatologist suspects laboratory error with an erroneously high reported serum bilirubin value.

If after 8 hours, the total serum bilirubin remains above the threshold value, an exchange transfusion should be performed. During this eight-hour period, the clinical staff will prepare to perform an exchange transfusion (including the type and cross match of the blood).

If the infant has direct hyperbilirubinemia (>2mg/dL), the decision whether to perform an exchange transfusion should be based on whether the indirect bilirubin level exceeds a value that is usually associated with a total serum bilirubin above the threshold level (indirect bilirubin exceeding either 12.0 or 14.0 mg/dL depending on birth weight category).

5. Would the proportion of ELBW infants who receive an exchange transfusion be expected to increase during the trial?

For the following reasons, exchange transfusions would **not** be expected to increase: A) In neonatal units, the bilirubin threshold for exchange transfusion for ELBW infants is set about 5 mg/dl higher than the phototherapy threshold, and exchange transfusions are performed infrequently; B) The higher the exchange level, the fewer the number of exchange transfusions that would be performed in the absence of any phototherapy; C) Similarly, the higher the exchange level the fewer the number of

exchange transfusions that would be expected with phototherapy started at given value (e.g. 5 mg/dL) below the exchange level. For these reasons, it would be expected that there would be fewer exchange transfusions among babies in the conservative phototherapy group (who had phototherapy started at 8 or 10 mg/dl and received an exchange transfusion at 13 or 15 mg/dl) than among infants of the same birth weight whose phototherapy was started at 5 and exchanged at 10 (as in some nurseries). Even if there were some additional exchange transfusions performed in the conservative phototherapy group relative to that in usual clinical practice this increase would be offset by a reduction in the aggressive phototherapy group who would be likely to have a lower threshold for phototherapy or a higher threshold for exchange transfusion than in most nurseries.

This reasoning is supported by the clinical experience in the Network center that was most conservative in treating hyperbilirubinemia at the time such treatment was last surveyed in the generic database (1997). By the treatment protocol in that center (UT Southwestern), phototherapy was routinely initiated for ELBW infants at a bilirubin value of 8 mg/dl if they were high risk and 11 mg/dl if they were low risk (by criteria similar to those in the Collaborative Phototherapy Trial). Exchange transfusion was performed at a threshold 5 mg/dl higher than that for initiation of phototherapy. This treatment regimen is comparable to that in the proposed study. The mean peak serum bilirubin for ELBW infants (10.5 mg/dl) was highest among Network centers and the proportion of ELBW infants who received phototherapy of any duration (80%) was lowest. An exchange transfusion was performed in only 1% of ELBW infants (range for other Network centers 0-2%). Also of note, the treatment protocol in this center in use in 1997 had been adopted in 1986. Clinical or postmortem findings suggesting bilirubin encephalopathy were rarely identified following adoption of this protocol. The favorable Network follow-up findings for this center also provide reassurance that neurodevelopmental impairment is not increased in this center.

6. Are baseline bilirubin measurements necessary? How often should serum bilirubin be measured? What should be done to control bias in ordering serum bilirubin determinations?

As discussed above, it is important to achieve substantial differences between groups in peak serum bilirubin levels and duration of phototherapy. A baseline serum bilirubin at the time of enrollment will be obtained in the first 100 infants enrolled in each cohort. In a randomized clinical trial where no differences between the groups should be found at enrollment this should be sufficient to establish a baseline serum bilirubin for each cohort. In the remainder of the infants any total serum bilirubin done within four hours prior to enrollment or the initiation of phototherapy will be recorded.

Partly for the sake of simplicity, the protocol does not prescribe detailed schedules for measuring the serum bilirubin for infants of a differing birth weight, postnatal age, serum bilirubin, and clinical condition. A problem with a completely unregulated approach is that clinician bias may influence the number of serum bilirubin determinations. For example, physicians concerned that conservative phototherapy increases the risk of handicap might be likely to order serum bilirubin determinations more frequently in the conservative phototherapy group than in the aggressive phototherapy group. Because of laboratory variation in serum bilirubin, ordering more

serum bilirubin determinations will by itself increase the measured peak serum bilirubin and the likelihood that the measured serum bilirubin will reach the threshold indication for phototherapy or exchange transfusion.

We propose the following to address this problem: 1) In assessing the effect of the two phototherapy protocols on the maximum serum bilirubin value, the two groups would be compared with respect to the serum bilirubin value closest to a specific time (9 am) each day, thereby preventing artifactual differences between groups in measured peak serum bilirubin as a result of differences in frequency of determinations. 2) At least one total serum bilirubin will be obtained each day for the first 7 days of life (DOL#1-7) in each infant. In addition during DOL #8-14 a TSB level will be obtained if the baby remains on phototherapy, if the phototherapy has been stopped in the past 24 hours (rebound), and if the previous TSB level was >7.0 mg/dl in infants with birth weight 750-1000 and >5.0 mg/dl in infants with birth weight 501-750. Obtaining determinations for this long is needed to assure that bilirubin is likely to be measured on the day that the bilirubin reaches its peak, particularly in the conservative phototherapy group where bilirubin values may well peak at a later age. (The mean age at peak serum bilirubin in Network centers when last recorded for the GDB in 1997 ranged from 6.0 days to 10.0 days. The value was 10.0 days in 2 centers, including UT Southwestern where the treatment of jaundice was most like the conservative phototherapy regimen. The SD in these 2 centers was 2.8 and 3.0 days, respectively.) Obtaining these determinations will also allow the two groups to be compared with respect to mean serum bilirubin for the first 7 days after enrollment and the amount of time the TSB level was over 8 mg/dl or 10 mg/dl. 3) Each center would define and use a standardized approach to the frequency of measuring serum bilirubin during the study. In centers where serum bilirubin is measured at no extra cost whenever serum electrolytes are ordered, serum bilirubin might simply be obtained as frequently as serum electrolytes. This approach would tailor the frequency to the maturity, age, and condition of the infant and would minimize bias in ordering serum bilirubin levels. Whatever approach is used in individual centers, the most important issue would be to assure comparable approaches to ordering serum bilirubin in the two groups of infants especially when bilirubin values approach the threshold for exchange transfusion. This is unlikely to be a difficult or important problem for the trial.

7. Should babies with detectable or severe hemolytic disease be excluded? If so, how would they be identified in a reliable and timely manner?

We have debated these questions at length and concluded that infants should be included unless they have severe hemolytic disease diagnosed in utero (e.g., infants with hydrops fetalis). In some centers, it would be difficult to identify Coombs positive infants in the first 12-24 hours after birth. There were also concerns about the proper interpretation and importance of a positive Coombs test. While the risk of bilirubin encephalopathy at a given serum bilirubin level may be higher in the presence of hemolytic disease than in its absence, this is an uncommon problem in ELBW infants. The incidence of Coombs positive hemolytic disease is approximately 3% in term infants and is probably lower in the ELBW population due to reduced transfer of maternal antibodies. An infant who is Coombs positive and has significant hemolytic disease identified after enrollment may be removed from the treatment protocol at the

attending's discretion and managed as desired. A secondary analysis can be performed with these infants excluded. All infants will be analyzed in an intention to treat analysis.

8. How long should the intervention protocol last?

This point was discussed at length. For the following reasons, we concluded that the treatment protocol should be used for the first 14 days: a) The peak total serum bilirubin is very likely to occur within the first 14 days. In1997 the median age at peak serum bilirubin was 3 days for all infants and as high as 7 days for the infants in two centers; b) Most clinicians would not use phototherapy to treat direct hyperbilirubinemia and peak serum bilirubin values occurring after 14 days because they are likely to be associated with elevated direct bilirubin values in infants receiving prolonged parenteral nutrition (The maximum values for the age at peak serum bilirubin exceeding 100 days in 3 centers); c) Most of what is known about phototherapy is based on observations in the first two weeks of life and the risk of encephalopathy at a given serum bilirubin level may well be lower after two weeks; d) We wanted to simplify data collection and the treatment protocol.

After 14 days, the treatment of elevated bilirubin levels would be left to the discretion of the attending neonatologist.

F. BACKGROUND/PREVIOUS STUDIES. See Statement of Problem and Rationale/ Justification.

G. METHOD/PROCEDURES

1) Study Design. A multi-center randomized intervention trial. While the clinical staff will not be blinded to treatment group, the follow-up examiners will be kept unaware of treatment group or peak total serum bilirubin.

2) Population.

Inclusion criteria:

1. 501-1000 grams BW
2. Admission to a NICHD Neonatal Network Center at an age that allows consent to be obtained and randomization performed no later than 36 hours after birth.

Exclusion criteria:

1. Death before enrollment is feasible.
2. Terminal condition- [pH <6.8 for > 2 hours OR persistent bradycardia (HR<100 bpm) associated with hypoxia for > 2 hours]
3. Prior use of phototherapy
4. Major congenital anomaly
5. Hydrops fetalis or severe hemolytic disease diagnosed in-utero
6. Overt congenital nonbacterial infection
7. Parental refusal or inability to provide consent
8. Attending physician refusal
9. Parents who are considered unlikely to return for follow-up evaluation. These would include mothers who were vacationing/visiting in the area, mothers who

are incarcerated, and mothers who indicate they are planning to move from the area.

3) Study Intervention

Consent would be obtained to allow randomization as soon as feasible within the period 12-36 hours after birth, preferably between 12 and 24 hours. Enrollment would occur at the time of randomization. Outborn infants would be included if they could be enrolled and randomized by 36 hours. Multiple births would be randomized individually (reference for appropriate statistical methods for analysis of infants randomized in this way to be provided). Randomization would be performed using a centralized phone system at RTI. Infants would be stratified according to birth weight and Center. The study intervention will last for 14 days.

Use of Phototherapy and Exchange Transfusion

Table 1- Guidelines for Initiating Phototherapy and Exchange Transfusions

Birth Weight	Aggressive Management		Conservative Management	
	Phototx Begins	Exchange Transfusion	Phototx Begins	Exchange Transfusion
501-750 gm	ASAP after enrollment	≥13.0 mg/dl	≥8.0 mg/dl	≥13.0 mg/dl
751-1,000 gm	ASAP after enrollment	≥15.0 mg/dl	≥10.0 mg/dl	≥15.0 mg/dl

Table 2- Guidelines for Stopping and Restarting Phototherapy

Birth Weight	Aggressive Management		Conservative Management	
	Phototx Restart/Stop DOL #1-7	Phototx Restart/Stop DOL #8-14	Phototx Restart/Stop DOL #1-7	Phototx Restart/Stop DOL #8-14
501-750 gm	5.0 mg/dl	5.0 mg/dl	8.0 mg/dl	8.0 mg/dl
751-1,000 gm	5.0 mg/dl	7.0 mg/dl	10.0 mg/dl	10.0 mg/dl

Exchange Transfusions- If the threshold value for exchange transfusion is reached, the attending neonatologist may defer exchange transfusion, administer intensive phototherapy for up to 8 hours, and repeat the serum bilirubin if:

a) the infant has not previously received phototherapy;
b) phototherapy has been provided in a manner that is considered inadequate; or
c) based on prior serum bilirubin values or clinical findings, the attending neonatologist suspects laboratory error with an erroneously high reported serum bilirubin value.

If after 8 hours, the total serum bilirubin remains above the threshold value, an exchange transfusion should be performed. Exchange transfusion should be deferred at that point only if the attending neonatologist concludes that the infant is too ill to tolerate the procedure. If the infant has direct hyperbilirubinemia (>2mg/dL), the decision whether to perform an exchange transfusion should be based on whether the indirect bilirubin level exceeds 12 mg/dL in infants between 501-750 gms and 14 mg/dL in infants between 751-1000 gms.

If an attending physician decides that an exchange transfusion is clinically indicated due to overt signs of kernicterus, significant hemolysis, or a rapidly rising total serum bilirubin level in a Coombs positive infant, then they should proceed with the exchange transfusion. This is outside of the current protocol, but would be a clinically indicated exchange transfusion.

Phototherapy- Standardized orders would be placed on the chart. Infants assigned to the aggressive phototherapy group would have phototherapy started as soon as feasible between 12 and 36 hours. Infants assigned to the conservative phototherapy group would be started on phototherapy when their serum bilirubin reached the threshold value for their birth weight. Phototherapy will be initiated and stopped or restarted at the levels noted in Tables 1 and 2. Once phototherapy is started it should be continued for a minimum of 24 hours. In the second week of life the stop and restart levels in the Aggressive cohort will be increased to 7 mg/dl only in the infants with birth weight 751-1000 gm. The levels for stopping and restarting in the Conservative cohort will remain the same in both weeks.

As long as direct hyperbilirubinemia was not present (>2 mg/dL), phototherapy would be restarted at any time that the total serum bilirubin level increased above the "threshold values" in either cohort up to 14 days.

Total serum bilirubin levels and other laboratory data- Infants enrolled in the study would have a total serum bilirubin measured each morning for 7 days. From DOL #8-14 a total serum bilirubin level will be drawn if the baby is on phototherapy, the phototherapy has been stopped in the past 24 hours, or if the previous TSB level was >5.0 mg/dl in infants with birth weight 501-750 gms and >7.0 mg/dl in infants with birth weight 751-1000 gms. The peak total serum bilirubin will be recorded each day if this is a different level from the total serum bilirubin closest to 9 a.m. The direct serum bilirubin will be recorded when available.

Baseline total serum bilirubin levels will be collected on the first 100 infants enrolled in each cohort. In the rest of the infants the total serum bilirubin level will be recorded if one was done within 4 hours of enrollment and within 4 hours of initiating phototherapy.

On DOL#5 $\pm$ 1 day, 0.3-0.5 cc of blood will be drawn in conjunction with a routine blood draw in that baby. The blood should be protected from light, centrifuged and frozen. It will be shipped in batched shipments to Dr. Bill Oh's laboratory at Brown University or to Dr. David Stevenson's laboratory at Stanford University. A total serum bilirubin, an unbound serum bilirubin, and an albumin level will be done on this specimen. Information on the baby's pH level, need for blood pressure support, need for CPR in past 24 hours, infection status, and hemolytic status will be recorded at the time the specimen is drawn. <u>This blood draw and specimen are optional. An infant may participate in the study if the parents refuse this portion of the protocol.</u>

The lowest pH level (if done) will be recorded each day. The first hematocrit done in the first 12 hours of life will be recorded. The mother's and baby's blood type and Coombs will be recorded. The administration of Phenobarbital will also be recorded.

Irradiance- The irradiance of the phototherapy used should be maintained above 15 $\mu W/cm^2/nm$ and below 40 $\mu W/cm^2/nm$ as measured at the umbilicus (supine) or lumbar spine (prone). The phototherapy lights should be adjusted to obtain these levels. Lights should not be moved closer than the manufacturer's recommendations. The infant's eyes should be patched. The baby should be naked with the diaper positioned to provide maximal skin exposure.

If phototherapy spotlights are used a Plexiglas filter or some other suitable filter should be maintained between the baby and the spotlight. This is due to concerns of increased levels of UVA radiation emitted by these lights. An incubator or isolette is an acceptable filter for UVA radiation.

If the baby is approaching exchange transfusion levels, then "double phototherapy" should be initiated by adding a biliblanket. If a biliblanket is not available, then a second bank of lights may be added. If the baby's TSB level is within 2mg/dl of an exchange transfusion, the attending may use phototherapy in the manner they think is most appropriate to avoid an exchange transfusion.

A Network nurse will measure the irradiance level and record the method of administering phototherapy (including the use of a "bili blanket" and/or number of banks of phototherapy lights once a day) on weekdays for all infants receiving phototherapy. This should be done at approximately the same time each day.

Co-interventions- Co-interventions including the management of fluids, thermal environment, antibiotics, ventilation, treatment of patent ductus arteriosus, and other issues would be determined by the procedures within Network Centers and the discretion of the attending neonatologist.

Length of Data Collection and Long Term Outcomes- Data will be collected and the thresholds will remain in effect for each treatment group through Day 14.

An automated ABR or diagnostic ABR will be done on every infant enrolled in the trial prior to discharge or transfer to a Level II facility. If an infant fails the automated ABR or diagnostic ABR, then further testing would be clinically mandated to rule out a significant hearing deficit. This testing would not be a part of the current protocol, but would be medically necessary. The results of this testing will be obtained and recorded. Results of OAE and/or ABR at discharge will be recorded for each ear as required by the GDB.

Infants would be followed per the GDB until death, 120 days of life or discharge. All infants would be followed in the Neonatal Follow-Up Network until 18-22 months

corrected age. The standardized protocol that is currently in use (or updated) will be performed on all infants at 18-22 months corrected age.

The **Data Safety Monitoring Committee** will review the progress of the study, data, and adverse event reports at 4 time points during the study. One of these time points will be when all enrolled infants have reached "status" or have been discharged from the NICU.

4) **Definitions of primary and secondary outcomes**.

a. Primary Outcome- Death and/or neurodevelopmental impairment at 18-22 months corrected age- Infant will have one or more of the following:
   i. Death
   ii. MDI <70
   iii. PDI <70
   iv. Cerebral palsy- Nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity with abnormal control of movement and posture.
   v. Blind- No functional vision in one or both eyes.
   vi. Deaf- Hearing disability which requires hearing aids
b. Secondary Outcomes will be defined using the GDB definitions or the Follow-Up Manual definitions.

5) Sample Size and Duration of Study

Enrollment will continue for two years or until the enrollment reaches 1,976 infants, whichever occurs last. As shown below, we conservatively estimate that the enrollment for the study could be completed within 2 years to evaluate a risk difference in the primary outcome of 7%, providing the number of ELBW infants in the current Network is not less than in the Network in 1999.

Based on the current GDB for the neonatal period and for follow-up assessments, we estimate that the proportion of infants who die or are impaired at 18-22 months will be at least 60% in the group with the higher proportion of such infants. We will design the study to identify a 53% or lower proportion in the group with a lower rate with a power of at least 0.8 and an alpha=0.05. To achieve a power of 0.80 we calculated that a total sample size of 1552 total infants whose primary outcome could be evaluated is necessary. As calculated below, we expect to randomize1,976 total infants in two years with 1,648 available for assessment of the primary outcome of death or neurodevelopmental impairment, affording slightly greater power than 0.80.

In the GDB from 1/1/99 to 12/31/99 there were about 1,700 total ELBW infants. A total of 14% die by 12 hours of life and we estimate another 3% would die before enrollment leaving 1,411 infants. We estimate that 30% of the infants will not be enrolled due to parental refusal or exclusion criteria. Therefore, approximately 988 infants would be enrolled and randomized each year in the study. Subtracting the mortality before 12 hours from the mortality before discharge, we estimate17% of those enrolled would die prior to discharge. Thus, approximately 820 infants would be discharged home per

year. Based on previous follow-up rates we would anticipate an 80% follow-up at 18-22 months or 656 infants per year who would be evaluated at 18-22 months. Thus, the number per year for whom the primary outcome would be assessable would be 656 (infants seen at follow-up) + 168 (infants who died prior to discharge)=824 infants per year or 1648 infants in 2 years. This indicates that based on the GDB data from 1999 that the necessary sample size (1976 infants) should be enrolled within 2 years without undue difficulty. The calculations are shown below:

1,700 Total ELBW infants in GDB *per year* (data of 1999)
- 289 Infants who die in first 24 hrs (17%) (data of 1999)
1,411 Potential infants for study
- 423 Ineligible infants or parental refusal, etc. (estimated at 30% of eligible infants)
988 Infants *total per year* randomized in both groups

988 Infants enrolled *per year*.
- 168 deaths before discharge (estimate by subtracting 17% above from GDB mortality
820 Infants discharged from hospital for follow-up
x .80 Follow-up rate (estimated, including known deaths following hospital discharge)
656 Infants *per year* who would be evaluated at follow-up

Based on recent estimates from the 2001 GDB, we would anticipate an annual enrollment of 1075 and 926 infants would be available for assessment of the primary outcome. If the study were continued for two years, this would increase the power to approximately 86%.

We also estimated the power for the outcome of death or moderate/severe impairment (MDI or PDI <85). Using a sample size of 926 in each group and an estimation of death or moderate/severe impairment of 78% (provided by Ken Poole from recent Network data), a reduction in this outcome to 71% would have a $\beta = 0.93$ using an $\alpha = 0.05$. For moderate/severe impairment alone, a 7% reduction from 61% to 54% would have a $\beta = 0.79$. For severe impairment alone (MDI or PDI <70), a 7% reduction from 46% to 39% would have a $\beta = 0.79$.

6) **Statistical Analyses**. Intention to treat analysis and standard statistical methods would be used. Categorical variables would be assessed by Chi Square or Fisher Exact Test. Continuous variables would be assessed by t test providing the assumptions of the test are satisfied. The primary analysis, will address whether the likelihood of death or impairment is related to treatment group, controlling only for center. An additional analysis will be conducted using logistic regression analyses in the dependent variable is the likelihood of death or impairment and the dependent variables are treatment group, center, and various measures of risk at baseline (e.g., BW, gestational age, sex, and perhaps ventilator settings and FiO_2 at randomization). Similar analyses will be conducted for the secondary outcomes. A $p < 0.05$ will be considered significant for analyses of the primary adverse outcome and for mortality alone. Given the large number of variables assessed, a $p<0.01$ will be considered significant for the remaining comparisons.

Statistical modeling will be used to assess the relationships between treatment, bilirubin exposure, and presence or absence of risk factors that may influence the risk of bilirubin toxicity at a given serum bilirubin level (e.g., sepsis, hypoalbuminemia, hemolytic disease, and acidosis). In conducting these analyses, statistical models will be developed in a randomly selected subset of all infants enrolled and validated in the remaining infants. Logistic regression analyses will be performed in which the dependent variable is the likelihood of an adverse outcome and the independent variables are treatment group, center, birth weight and other base line variables at randomization, a measure of bilirubin exposure [e.g. peak serum bilirubin or duration of serum bilirubin above a particular value], and whether the infant is low or high risk according to the risk factors noted above. Acidosis, for example, will be assessed in models to address questions such as "Is the risk of a given peak serum bilirubin level related to the lowest prior pH?" and "Is the risk of a given peak serum bilirubin related to the lowest pH on the day that the bilirubin value occurs?")

Interaction terms will also be included in the regression equations and may identify clinically important relationships. For example, An interaction between treatment group and risk group (high or low) may occur if aggressive phototherapy was beneficial only in the high-risk infants of a given birth weight. An interaction between treatment group and birth weight may occur if aggressive phototherapy (as defined in this trial) was beneficial only in the smallest infants. An interaction between treatment group and peak serum bilirubin may occur if the risk at a given peak serum bilirubin is influenced treatment group (e.g., if the conversion of bilirubin to nontoxic photoisomers reduces the risk at a given total bilirubin in phototherapy treated infants).

If there is evidence of toxicity from phototherapy, similar types of models would be used in assessing the relationship between the use and the duration of phototherapy to the likelihood of an adverse outcome.

7) Tables.

Tables like those below indicate the sort of data tables that would be planned for the primary publication.

Characteristics At or Before Enrollment

	Aggressive	Conservative
Birth Weight		
Gest Age		
Male		
Caucasian		
Black		
Hispanic		

Other		
Inborn		
C-section		
Apgar at 5 min		
Resp. status at 24 h MAP FiO_2		
Initial Hct		
Coombs + Mom		
Coombs + Baby		

Bilirubin Levels and Therapeutic Results

	Aggressive	Conservative	P value
TSB Baseline			
TSB at enrollment			
TSB at start of Phototherapy			
Peak TSB			
Mean TSB in 1st 7 days (of values closest to 9am)			
Age (hr) at Peak			
Age PTx Started (hours)			
Duration of PTx (hours)			
Exchange transfusions (N %)			
Irradiance level			
Banks or Blankets/Day			

Medical Complications and Length of Stay

	Aggressive	Conservative	RR, CI
IVH 1 and 2; 3 and 4			
CLD at 36 wks			

PDA- ligated or indocin treated			
NEC			
ROP			
Late Onset Sepsis			
Days to regain BW			
Deaths prior to d/c			
A-ABR at discharge			
Length of stay			

Mortality and Neurodevelopmental Outcome at 18-22 months Corrected (n, % of infants randomized)

	Aggressive	Conservative	RR, CI
Known deaths to 18-22 m			
Lost to follow-up			
Death or Impairment*			
Impairment*			
Cerebral palsy			
Athetoid movement			
Blind			
Deaf			
Bayley MDI (mean)			
Bayley PDI (mean)			
Bayley MDI <70 (%)			
Bayley PDI <70 (%)			
Bayley MDI <85			
Bayley PDI <85			
Walks fluently			
Seizures			
Weight < 5th%			
FOC <5th%			

*Impaired= Bayley MDI or PDI <70, CP, blind or deaf

8)Available population/compatibility with other ongoing protocols.

With the exception of the Preemie INO study and the Benchmarking Trial, there are no other interventional studies that have been approved by the Steering Committee that would involve the same population and that would be ongoing at the time this trial could be initiated. The proposed trial would not be expected to compromise the feasibility or validity of these two studies or other studies that have been proposed.

9) Estimate of projected recruitment time.

We estimate that study enrollment could be completed in 2 years. Another two years would be needed to complete the follow-up assessments. We would propose that enrollment be continued for two years or until 1976 infants have been enrolled whichever is later. This would establish a predefined stopping time and might increase the power of the study if more infants could be enrolled in the two-year period.

10) Risks/benefits with estimate of frequency/severity of risks.

No experimental therapies or evaluation procedures will be used in the study. Because of the uncertainty about the appropriate indications and the risks and benefits of phototherapy, there is no discernible increased risk for participation in the study. There is the potential benefit with the increased attention to monitoring and follow-up evaluation.

11) Costs of study

The incremental costs of the study above usual costs for care, generic data collection and follow-up assessments would include the costs for serum bilirubin measurements that would not otherwise be performed, spectroradiometers for each center, automated ABRs at discharge or prior to transfer, and the personnel time for obtaining consent and randomization, measuring and recording irradiance levels for infants receiving phototherapy, and recording the duration of phototherapy and number of any exchange transfusions.

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SAMPLE CONSENT FORM

A Comparison of Phototherapy Treatments for Extremely Low Birth Weight Infants

INVITATION TO PARTICIPATE

You, as a parent or legal guardian of _____, are invited to enter your child into a research study conducted at the _____. As explained below, this is a study of phototherapy (placing babies under blue lights), which has been used for more than 30 years to treat babies with jaundice (yellow skin color). Almost all babies as small as yours are treated with phototherapy.

This study will be supervised by _____(doctors who specialize in the care of sick or premature babies). Your decision to permit your child to participate is voluntary and may be withdrawn at any time. Refusal to participate in this study or withdrawal at a later date will not affect the care given to your child by your physician or any other health professionals. This study has been approved by the Committee for the Protection of Human Subjects _____, an independent committee to help assure that research studies are safe and properly performed.

PURPOSE OF THE STUDY

This study will help doctors learn when phototherapy should be started for babies as small as yours. Phototherapy reduces the amount of bilirubin in the blood. Bilirubin is a substance that causes jaundice and, in high levels, can cause damage to the brain. Doctors don't know how high the bilirubin level must be to cause problems. Phototherapy reduces the bilirubin level but, like all treatments, can cause problems. It is known to have temporary and minor side effects that don't usually cause major difficulty. It might also cause some bad effects that have not been identified even though it has been used for many years.

Some doctors start phototherapy within two days of birth and some start phototherapy only later when the bilirubin level is higher. It is not known which treatment method is better in very small premature infants.

This study will compare these two different methods of phototherapy treatment and determine whether they affect the bilirubin levels, the number of infants who have problems in the nursery, and the number of infants who have problems with mental and motor skills at about 2 years of age. This information will help doctors better understand the effects of phototherapy and bilirubin.

DESCRIPTION OF THE STUDY

If you agree that your baby will be included, your baby will be treated in one of two ways--either starting phototherapy within the first 36 hours after birth or waiting to start phototherapy until the bilirubin has increased somewhat. Some doctors prefer the first method, others the second method. No one knows for sure which is better. Which method your baby will receive will be decided by chance (like a flip of a coin). If your baby is assigned to the Aggressive group, the phototherapy will be started immediately. If your baby is assigned to the Conservative group, the phototherapy will be started when and if your baby's bilirubin level reaches a certain level. Research nurses will record the daily bilirubin levels and the amount of acid in the blood. The initial blood count and blood type of the blood will be recorded once. These values will be taken from routine lab results. The amount of phototherapy that your baby receives will also be recorded. When your baby is about 5 days old a small amount of blood will be drawn to look at the amount of free bilirubin and albumin (a protein) in the blood. This sample will be labeled in a confidential

manner and sent to a lab at _____ to be tested. All babies will receive a hearing screen at discharge or before transfer to another hospital. The results of your baby's hearing screen will be recorded.

After discharge your baby will return to a special follow-up clinic for small babies like yours. This clinic is specially designed to provide care for former premature infants. At 18-22 months corrected age your baby will receive as part of the study a complete exam of their muscles, nerves, and mental and motor skills. These follow-up tests are a very important part of the study.

In order to successfully evaluate phototherapy, Dr. _____ and his/her associates will want to collect information about your baby's general health, hearing tests, and any hospitalizations during the first 24 months of life. By agreeing to participate in this study, you give consent for the release of medical records from those medical facilities and providers of medical care to Dr. _____ and his associates.

TIME COMMITMENT

This study begins with your agreement to allow your baby to participate in this study. During the initial hospitalization there is no time commitment required from parents. At 18-22 months corrected age your baby will receive an examination, developmental testing, and hearing testing as described. That clinic visit takes approximately 2-4 hours. You will receive _____ for participating in that visit.

BENEFITS AND RISKS

Your baby is likely to be treated with phototherapy whether or not you participate in this study. It is not known whether one method of using phototherapy treatment is better than the other. There are no extra risks other than those involved in the use of phototherapy. There may or may not be any extra benefits for your infant by taking part in this research. You will be told about any new information that becomes available during this research that might influence your decision to allow your baby to take part as a subject

ALTERNATE PROCEDURES OR TREATMENTS

This study is voluntary. If you choose not to have your baby participate in the project, he/she will continue to receive routine care. Phototherapy is likely to be included in routine care to reduce bilirubin levels in your baby.

COMPENSATION FOR INJURY

There will be no added expenses for your child's participation in this research. In the unlikely event of physical injury resulting from your baby's participation in this research understand that the _____, and those individuals conducting this study will not provide monetary compensation or free medical treatment for physical injury to your baby resulting from this research study. Necessary medical treatment will be provided to you and billed as part of your medical expenses. You understand that costs not covered by your health care insurer will be your responsibility. You understand also that it is your responsibility to determine the extent of your health care coverage.

CONFIDENTIALITY

Information about what the doctors learn from this study may be published or given to other people doing research, but neither your name nor your child's name will be used. Information gathered on your child as part of this study will be part of his/her medical record and will otherwise be confidential to the extent permitted by law.

You are making a decision whether or not to voluntarily participate in this study. You should not sign until you understand all the information presented in the previous pages and until all your questions about the research have been answered to your satisfaction. If you have any additional questions regarding this study

_____or one of the research nurses will be available to answer them for you at any time. You may contact them at _____.

Your signature indicates that you have decided to allow your son/daughter to participate having read (or been read) the information provided above. If you have any questions as to your son/daughter's participation as a research subject, call the Committee for the Protection of Human Subjects at _____. If you decide to participate in this research study, a copy of this document will be given to you.

_____ _____
Parent/guardian signature Date

_____ _____
Witness Date

_____ _____
Person obtaining consent Date

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
Updated March 28, 2005

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 (±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 (≤ 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 ≥ 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 ≥ 88% with an FiO2 ≤ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate ≤ ~~15~~ 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, air leak)

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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 ≥ 88% (using the altered Pulse Oximeters) for one hour
- A ~~n arterial~~ $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) ~~for 2 successive~~on a single blood gas~~es 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.

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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.

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CONTROL- Prophylactic/Early Surfactant and Ventilation

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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 ≤ ~~15~~ 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.

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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%

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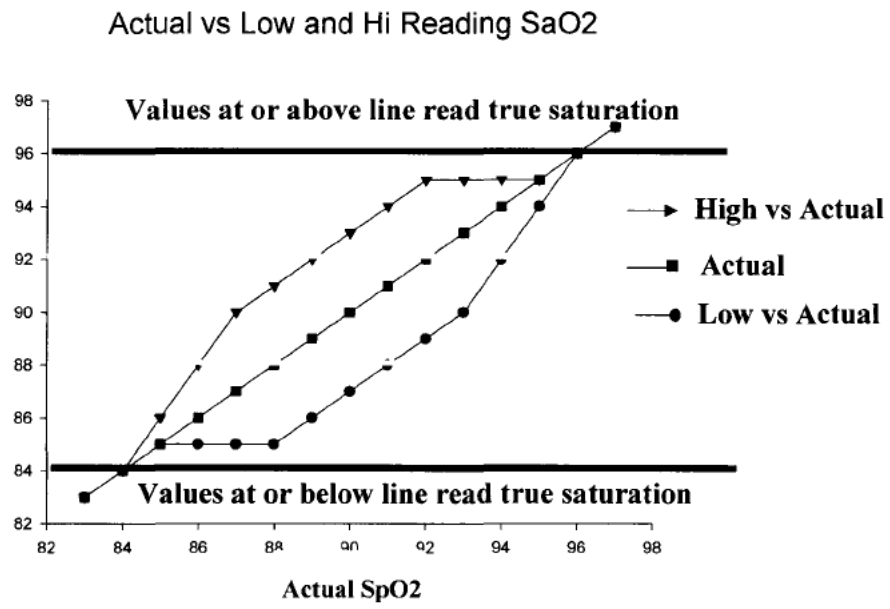
The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will 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.



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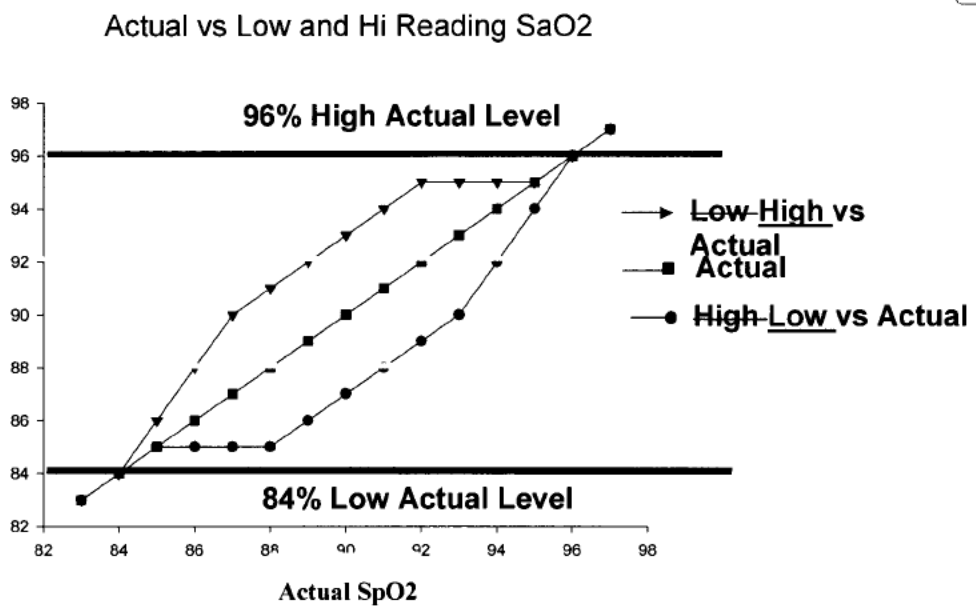

Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent 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;

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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.

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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

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- 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

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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

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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.

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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		
		Low	High	Overall
CPAP	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		
		Low	High	Overall
CPAP	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		
		Low	High	Overall
CPAP	Yes	25	35	30
	No	35	45	40
	Overall	30	40	35

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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)			

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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 ≤ ~~15~~ 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 ≤ ~~15~~ 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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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

Protocol for the NICHD Neonatal Research Network

RANDOMIZED CLINICAL TRIAL OF INHALED PGE_1 IN NEONATAL HYPOXEMIC RESPIRATORY FAILURE

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1.0 ABSTRACT

Hypoxemic respiratory failure (HRF) in the newborn is usually associated with widespread vasoconstriction of the pulmonary microvasculature giving rise to intra- and extra-pulmonary shunts and profound hypoxemia. The goal of therapy is to decrease the regional pulmonary vascular resistance of ventilated lung areas thus decreasing intrapulmonary shunting and selectively reducing the pulmonary-artery pressure without causing systemic vasodilation. Intravenously administered vasodilators lack pulmonary selectivity leading to systemic side effects. Inhaled nitric oxide (INO), a selective pulmonary vasodilator, has revolutionized the treatment of respiratory failure in the newborn. However, there is lack of sustained improvement in 30-46% of infants (1-4); moreover, INO requires specialized monitoring and scavenging systems for administration, making the treatment expensive and limiting availability. Aerosolized prostaglandins I_2 and E_1 have been reported to be effective selective pulmonary vasodilators in animals and human adults (5-19). In addition, inhaled PGI_2 ($IPGI_2$) has also been reported to be effective in preterm and term newborns, and children with pulmonary hypertension (20-26). Although intravenous PGE_1 is widely used in neonates, the use of the inhaled form has not been reported in newborns with pulmonary hypertension. Compared to PGI_2, PGE_1 has a shorter half-life, lower pKa (6.3 versus 10.5), bronchodilator action, anti-proliferative and anti-inflammatory effects on the alveolar, interstitial and vascular spaces of the lung (17, 27-31). Prostaglandin nebulization can be used without the sophisticated technical equipment needed for controlled NO inhalation and hence is less expensive. It has no known toxic metabolites or toxic effects. Prostaglandins and nitric oxide relax the vascular smooth muscles through two different second-messenger systems; therefore, in combination, INO and $IPGE_1$ may have synergistic effect (32). The existing literature suggests that inhaled PGE_1 is a potential effective vasodilator in the treatment of HRF of the newborn. We have recently reported the safety and feasibility of short-term administration of inhaled PGE_1 in an un-blinded Phase I/II dose-escalation study. Of the 4 doses tested in the Phase 1/II trial, we have defined two doses that are most likely to be effective without causing adverse effects. In the current protocol, we propose a pilot to evaluate the feasibility and safety of prolonged $IPGE_1$ in neonatal HRF. Two doses of $IPGE_1$ (300 and 150 ng/kg/min) will be administered over a maximum duration of 72 hours to determine feasibility, safety, optimal dose and duration of therapy in 50 patients in 9 NICHD NRN sites. The total budget for study is $60,000 and will be covered by Dr. Sood's K23 award ($40,000) and the Wayne State University site (Children's Hospital of Michigan $20,000).

2.0 PILOT RANDOMIZED CONTROLLED TRIAL

2.1 Study Hypotheses

We propose the implementation of a randomized controlled trial on the use of $IPGE_1$ in neonatal HRF. Fifty patients recruited at 9 high volume sites within the NICHD Neonatal Research Network will constitute a pilot sample to evaluate the feasibility and safety of prolonged $IPGE_1$ administration and determination of optimal dose. In this Pilot RCT, two doses of $IPGE_1$ (300 and 150 ng/kg/min) will be administered over a maximum duration of 72 hours. Once feasibility and safety of $IPGE_1$ administered over 72 hours has been demonstrated in the pilot trial, a full scale randomized controlled trial will be planned.

2.2 Primary Aims

2.2.1 To evaluate the feasibility of performing a RCT of the use of IPGE1 in neonatal HRF. We define feasibility for this pilot RCT as the ability to identify and randomize a sufficient number of patients to the study intervention within a reasonable time period and to demonstrate that the study can be initiated as planned without excessive protocol violations (more than 20%). This includes determination of the ability to identify eligible infants, obtain informed consent, and prepare, deliver and wean aerosolized study medication over a maximum duration of 72 hours in accordance with the study protocol, without serious adverse events and excessive protocol violations over a 6-9 month period.

2.2.2 To establish safety of IPGE1 when given over a longer duration. This includes the ability to safely administer and wean the $IPGE_1$ without protocol deviations or without evidence of any drug toxicity or severe adverse events. Safety will be assessed by monitoring hemodynamic parameters prior to, during and after study drug administration. Incidence of hypotension requiring treatment, upto 30% higher in the treatment compared to control group, will be considered acceptable.

2.3 Secondary Aims

2.3.1 To identify the optimal dose of IPGE1 in the treatment of neonatal HRF. On the basis of the previously published phase I/II unblinded safety and dose-escalation trial, we have identified 2 doses that are associated with a favorable response without adverse effects in the majority of patients when administered for 30 minutes each. These two doses, in addition to a placebo will be administered to the patients enrolled in the pilot RCT for a longer period of time (maximum duration of 72 hours) to assess the dose associated with the best efficacy and safety profile.

2.3.2 To define the optimal duration of therapy with IPGE1 in neonatal HRF. In the open-label phase I/II dose-escalation and safety trial, four doses of $IPGE_1$ were administered over a total period of 3 hours. Administration for a longer period is necessary in the clinical setting. Intravenously administered PGE_1 is used in newborns with ductal dependent congenital heart disease for several days to even months. We propose the administration of $IPGE_1$ for a maximum duration of 72 hours to assess safety of long-term administration, optimal duration of treatment, evidence for tachyphylaxis or cumulative toxicity.

2.3.3 Evaluation of efficacy of IPGE1 in Neonatal HRF. This is a secondary goal for the pilot RCT as we do not expect that a sample of 50 patients will be statistically adequate to address this question. However, we expect that the results of the Pilot RCT will provide evidence to support the use of "progression of an OI to $\geq$ 25" as the primary outcome variable for the full-scale RCT. Furthermore, these results will be important for the calculation of sample size for the full-scale trial. We expect a relative risk of 67% (range 50-80%) for the treatment compared to the control arm for progression of OI

to ≥25 in 50 patients recruited over a time period of 6-9 months to be able to justify embarking upon the full scale RCT.

3.0 BACKGROUND AND SIGNIFICANCE

3.1 Transition from Fetal to Neonatal Circulation

3.1.1 Role of Prostaglandins (PG's) and Nitric Oxide (NO)

Immediately after birth, the pulmonary vasculature starts to develop changes to affect an abrupt decrease in pulmonary vascular resistance. The mediators of neonatal pulmonary vasodilation include mechanical factors relating to stretching of the lung, an increase in oxygen tension, and vascular endothelial factors (Figure 1).

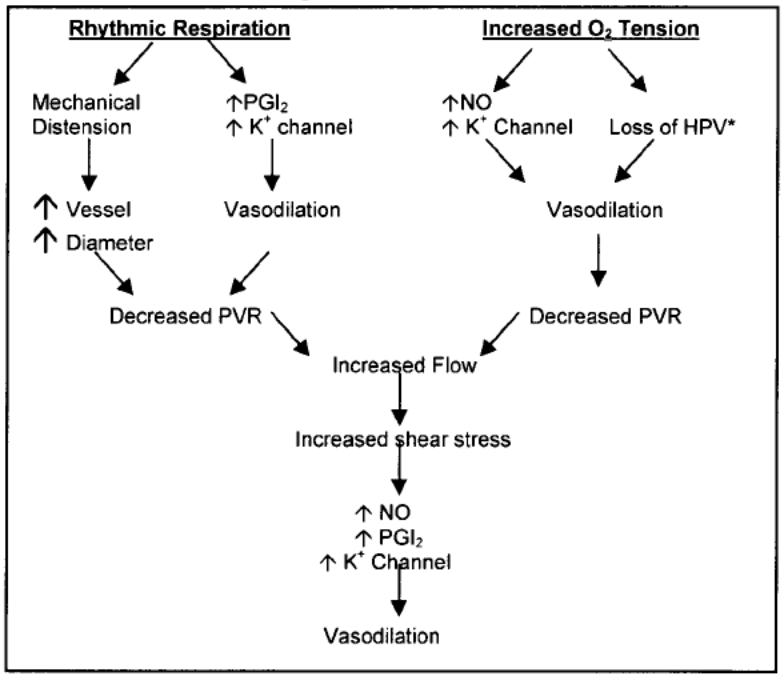


Figure 1. Birth related stimuli that lead to decreased pulmonary vascular resistance (From (33))
*HPV Hypoxemic pulmonary vasoconstriction

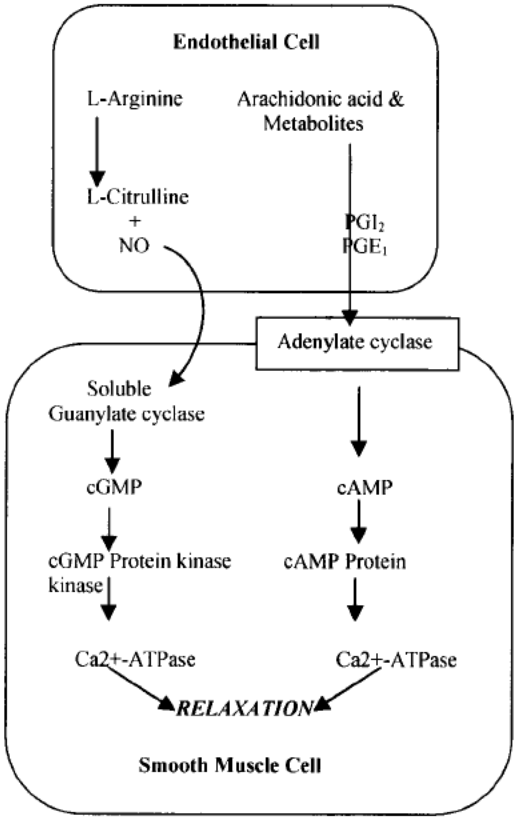


Figure 2. Second messenger systems in pulmonary vasodilation by NO and PGs

Arachidonic acid metabolites play a significant role in regulation of the transitional circulation. Prostacyclin (PGI_2) and PGE_1 are naturally occurring prostaglandin's produced in the walls of the blood vessels of mammalian species. It has been shown that PGI_2 production increases soon after birth and falls 2 to 5 hours later. PGI_2 participates in reduction of the PVR accompanying ventilation, but it is not found to be essential for maintaining low PVR once the low tone has been established. One of the theories on the pathophysiology of pulmonary hypertension is a mismatch of the thromboxane-prostacyclin ratio in lung endothelium (34). Hammerman et al measured plasma thromboxane B_2 (the stable degradation product of thromboxane A_2), levels in 14 human neonates with HRF and in 6 control infants (35). Thirteen of the 14 infants with PPHN had markedly elevated levels (1968 ± 1654 pg/ml), whereas none of the control infants demonstrated elevations (365 ± 291 pg/ml) ($p < 0.05$). Nitric Oxide (NO) also appears

to play an important role in reducing pulmonary artery pressure (PAP), thereby increasing the pulmonary blood flow (PBF). NO and PGI_2 may have synergistic effects in inducing postnatal pulmonary vasodilation as they relax the vascular smooth muscles through two different second-messenger systems (Figure 2); PGI_2 stimulates the cAMP pathway, whereas NO activates the cGMP pathway.

3.1.2 Neonatal HRF and Persistent Pulmonary Hypertension of the Newborn (PPHN)

HRF is a frustrating and sometimes, lethal complication of the transition to extrauterine life. It is associated with widespread vasoconstriction of the pulmonary microvasculature giving rise to intra- and extra-pulmonary shunts and profound hypoxemia. This clinical syndrome has also been referred to as persistent pulmonary hypertension of the newborn (PPHN) because of the failure of the elevated PVR to decrease postnatally in affected infants. HRF may result from a variety of neonatal diseases, such as meconium aspiration, group B streptococcal sepsis, congenital diaphragmatic hernia, or respiratory distress syndrome. Less commonly, HRF of the newborn may be idiopathic. It occurs in approximately 2% to 9% of infants admitted to neonatal intensive care units (36) and results in significant morbidity and mortality. It is well recognized that in the absence of congenital malformations of the lung, this condition will often improve if the patient can be supported while the pulmonary vascular resistance is most volatile. During this period PVR often exceeds systemic vascular resistance (SVR). Support may be required for a period of days to weeks.

3.2 Therapeutic Options

3.2.1 Conventional Management

At this point, the management of neonatal HRF remains empiric and supportive rather than curative. There have been few prospective randomized trials of most of the therapeutic modalities (NO and ECMO excepted) advocated for treatment of neonatal HRF and no trials of ventilatory techniques. Although *hyperventilation* is used as the standard approach to neonatal HRF by 81% of neonatologists (37), there is concern of acute and chronic pulmonary complications (38), impaired cerebral perfusion (39-41) and neurosensory deafness at extremes of alkalosis (42). Cornish, 1987 (43) and deLemos, 1992 (44), reported the successful use of *high frequency oscillatory ventilation (HFOV)* in infants with neonatal HRF. No studies have evaluated the efficacy of induced *metabolic alkalosis* in human infants (37). In a multicenter prospective observational study, it was demonstrated that alkali infusion is associated with increased risk for the use of ECMO and prolonged oxygen dependence (45). Systemic *vasopressors* may improve cardiac contractility and cardiac output. *Exogenous surfactant* treatment is a promising adjunctive treatment for near-term neonates and term neonates with pneumonia and meconium aspiration syndrome (46). The specific treatment for neonatal HRF involves *selective relaxation of the pulmonary vasculature.*

3.2.2 Pulmonary Vasodilators in the Treatment of Neonatal HRF

Despite the availability of multiple potent *intravenous vasodilators* such as tolazoline, prostacyclin, prostaglandin E, nitroprusside, and nitroglycerin, consistent reversal of the pulmonary vasoconstriction is elusive because of lack of pulmonary selectivity. Systemic vasodilation from these agents often leads to hypotension (30 to 60% of infants) (36), compromised tissue perfusion, and inadequate oxygen delivery to vital organs. In addition, due to nonselective vasodilation in well-ventilated and non- or poorly-ventilated lung units, the arterial oxygenation may worsen because of significant increase in shunt fraction (11%) (47). Therefore *vasodilators that affect the pulmonary vasculature selectively* are appealing adjuncts in the treatment of HRF.

3.2.3 Selective Pulmonary Vasodilators: Nitric Oxide (NO)

Inhaled NO is unique in its ability to lower PVR and PAP selectively in adults and infants with pulmonary hypertension. Due to the inhaled route, the vasodilatory property is restricted to well-ventilated lung areas, effecting a redistribution of blood flow from nonventilated regions to these areas. However, 30 to 40% of infants with PPHN do not respond to inhaled NO (1-4). Furthermore, INO being

a highly toxic molecule results in the production of methemoglobin and higher oxides of nitrogen, thus requiring specialized delivery systems and monitoring making treatment both expensive and limiting its availability (14).

3.2.4 Selective Pulmonary Vasodilators: Aerosolized Prostaglandins

Prostaglandins were first discovered in 1933 by von Euler and are now known to play a role in the pathogenesis and therapy of various lung diseases. Prostacyclin (PGI_2) and alprostadil (PGE_1) are naturally occurring prostaglandins with similar structure and short half-lives. Both prostacyclin and PGE_1 are potent vasodilators, and continuous intravenous infusions are required for safe administration. They are considered relatively safe even when used in critically ill patients as adverse effects disappear shortly after discontinuation.

The successful use of aerosolized PGI_2 in patients with ARDS and pneumonia was first reported by Walmrath et al in 1993 (48). The same authors later demonstrated that inhaled PGI_2 and PGE_1 were as effective as inhalation of NO in relieving pulmonary hypertension in an isolated rabbit lung model (13). In 1998, Putensen et al, reported comparable improvement of PVR and gas exchange in adult patients with ARDS using aerosolized PGE_1 or inhaled NO (18). These findings indicate that aerosolized PG's, like inhaled NO, selectively dilate blood vessels in ventilated lung areas, leaving regional vasoconstriction in non or poorly ventilated lung units unaffected thus improving arterial blood oxygenation by redistributing blood flow from essentially non-ventilated to ventilated lung units. This situation is analogous to the use of intravenous nitrosovasodilators i.e. nitroprusside, nitroglycerin, and organic nitrates - which cause release of NO as their mode of action but are not as efficacious as NO itself delivered by the inhaled route (46).

Prostaglandins have been in clinical use for more than 15 years - no toxic effects have been reported. Therefore, the risk of inhalational administration appears to be low. Devices for drug inhalation in ventilated patients are commonly available (22).

Aerosolized prostaglandins I_2 and E_1 have been reported to be effective selective pulmonary vasodilators in animals and human adults (5-19) (Appendix I). In addition, inhaled PGI_2 ($IPGI_2$) has also been reported to be effective in preterm and term newborns and children with pulmonary hypertension (20-26) (Appendix I). De Jaegere et al (20) reported improved oxygenation without adverse systemic effects in 4 preterm infants following endotracheal instillation of PGI_2. Similar beneficial effects were reported by Soditt et al in a preterm newborn with pulmonary hypertension (21). Improvement in oxygenation in 2 term infants with persistent pulmonary hypertension and one infant with congenital heart disease following administration of aerosolized PGI_2 has also been reported (22, 24). Kelly et al administered $IPGI_2$ and milrinone to 4 term infants who had failed to respond to INO with sustained improvement in oxygenation in 3 (23). In all studies, the inhaled application of either PGI_2 or PGE_1 proved to reliably lower pulmonary artery pressure without affecting systemic hemodynamics, especially without lowering systemic vascular index (49). Further the inhaled application of prostaglandins does not cause any harm to the airway, even when given over a prolonged period of time (50, 51). Thus, the inhaled route of prostaglandin administration in pulmonary hypertension seems to be as effective as the intravenous route in terms of lowering PVR but without the negative side effects, such as increased pulmonary shunting, reduced arterial oxygenation, or systemic vasodilation (49).

Although intravenous PGE_1 is widely used in neonates, the use of the inhaled form has not been reported in newborns with pulmonary hypertension.

3.2.5 Aerosolized Prostaglandins versus Nitric Oxide

Aerosolized PGI_2 has similar pulmonary vasodilating effects as inhaled NO but it also results in vasodilation of splanchnic vessels which increases gut perfusion (52). This phenomenon may be beneficial in patients with sepsis and may be explained by the longer half-life of prostacyclin associated with spillover into the systemic circulation. *Inhaled NO* confines its action to the pulmonary vessels because of instantaneous binding to hemoglobin. Rapid deactivation of PGE_1 in the lung endothelium may explain absence of systemic vascular effects during *PGE_1 inhalation*. Prostaglandin nebulization can be used without the sophisticated technical equipment needed for controlled NO inhalation. It has no

known toxic metabolites or toxic effects. Its only potential adverse effect is reversible systemic hypotension which is easily monitored in the ICU (47, 53).

3.2.6 Synergistic Effect of Prostaglandins and Nitric Oxide in Pulmonary Vasodilation

Parker et al, 1997, reported that combined use of *intravenous* prostacyclin (PGI_2)(8 ng/kg/min) and iNO (20 ppm) in a term newborn more effectively lowered systolic PAP than did either agent alone (54). However, there was an inevitable decrease in systemic arterial pressure (SAP) because of the intravenous PGI_2 effects on systemic circulation. Ikeda et al directly measured internal diameter changes in small pulmonary vessels in response to inhalations of *aerosolized* PGI_2 (25, 250, and 2,500 ng/kg/min), or NO (4 and 34 ppm), as well as the combination of aerosolized PGI_2 and NO in anesthetized cats (55). They found that the combination of these drugs produces a more enhanced vasodilator effect compared to their separate effects and induces maximum dilated states. This synergistic effect on PVR may be explained by the fact that these agents relax the vascular smooth muscles through two different second-messenger systems; PGI_2 stimulates the cAMP pathway, whereas NO activates the cGMP pathway (Figure 2). The combined effect of inhaled NO and PGI_2 was comparable to the maximal effect of the smooth muscle relaxant papaverine, which relaxes vascular smooth muscles by inhibiting cyclic nucleotide phosphodiesterases and accumulating both cAMP and cGMP. These findings suggest that the combination of NO and PGI_2 is able to induce maximum dilated states in small pulmonary vessels.

3.2.7 Prostaglandin E_1 versus Prostaglandin I_2

PGE_1 is a much less *potent vasodilator* than prostacyclin and higher doses are necessary to achieve similar pharmacologic effects. However, in a sheep model with induced pulmonary artery hypertension (using a thromboxane A_2 mimetic), a larger decrease in PVR was observed during PGE_1 than PGI_2 infusion suggesting that PGE_1 has greater pulmonary specificity than PGI_2 (35).

PGI_2 is the most potent endogenous *inhibitor of platelet aggregation*. This effect is short lasting in vivo disappearing within 30 minutes of cessation of intravenous administration. PGE_1 also inhibits platelet aggregation but is much less potent and shorter acting than PGI_2. PGI_2 production by the endothelial cells in the lung may be a defensive mechanism for dispersion of platelet aggregates in the small pulmonary vessels (56).

PGE_1 also has *bronchodilator effects* (17) whereas PGI_2 is a bronchoconstrictor. Inhaled NO also has bronchodilator action and this might improve ventilation/perfusion ratio.

PGE_1 has *anti-inflammatory and anti-proliferative effects*. It inhibits macrophage activation, neutrophil chemotaxis, and release of oxygen radicals and lysosomal enzymes (30, 57). It has been speculated that the reduction in reactive oxygen species production and neutrophil phagocytosis and chemotaxis by PGE_1 may contribute to the effectiveness of the drug in ARDS (17). PGE is also capable of suppressing mesenchymal cell proliferation in vitro (30).

One possible advantage of PGE_1 over prostacyclin as a pulmonary vasodilator is the shorter *half-life*. After intravenous administration, PGI_2 has a half life of 2 to 3 min. Intravenously administered PGE_1 has a half-life of 30 seconds or less in humans (58). PGE_1 is metabolized in the lung by 15-hydroxyprostaglandin dehydrogenase present in the lungs. This may contribute to its relative shorter half-life and *selectivity as a pulmonary vasodilator* (35). In patients with normal respiratory function, 70 to 90% of a dose may be metabolized in one pass through the lung (17). This is borne out by Borok's study (30) in which inhalation of up to 5 mg PGE_1 in a sheep model increased the PGE_1 concentration in the epithelial lining fluid without changes in the plasma PGE_1 concentrations and systemic hypotension. Although PGE_1 has a high pulmonary clearance in normal lungs, the pulmonary clearance may be markedly decreased in patients with severely diseased lungs - however, non pulmonary clearance processes appear to keep the plasma levels of the drug from becoming extraordinarily high (58). This is borne out by Meyer's study (17) in which no systemic adverse effects were seen in a series of 15 adult patients with acute lung injury. Significantly lower doses of inhaled PGE_1 are required to achieve pulmonary vasodilation comparable to that achieved during PGE_1 infusion reflecting the efficiency of alveolar prostaglandin delivery (18).

A concern with the use of inhaled aerosolized prostacyclin is the high alkalinity (pH = 10.5 ± 0.3) of the *buffer* in which the PGI_2 is diluted prior to aerosolization (Van Heerden, 1996). Habler et al (50, 51) demonstrated no evidence of pulmonary inflammation on prolonged administration of aerosolized PGI_2 in healthy lambs. PGE_1 is a stable compound at neutral pH (pKa of 6.3) and is diluted in normal saline for delivery as an aerosol.

The metabolic fate of PGE_1 in man has not been fully elucidated. 15-keto- PGE_1, 15-keto-13,14-dihydro- PGE_1, and PGE-M have been identified as major and biologically inactive metabolites of PGE_1. 13, 14-dihydro- PGE_1 has recently been demonstrated as an active metabolite with vasodilator and desaggregating properties similar to those of the parent compound (59).

To our knowledge, unlike nitric oxide, cytotoxicity has not been reported for inhaled prostaglandins. The present data suggest that inhaled PGE_1 is a potential effective vasodilator in the treatment of pulmonary hypertension of the newborn, however, no clinical reports have been published describing inhaled PGE_1 for the treatment of HRF in the newborn.

3.2.8 Inhaled drug delivery in mechanically ventilated-patients

The principles involved in aerosol delivery to mechanically ventilated patients have evolved over the past 15 years (60). The scientific basis for administering inhaled therapies to mechanically ventilated patients is now firmly established. The indications for inhaled therapies are rapidly expanding. The *advantages of inhaled therapy* include direct delivery of drug to site of action, rapid onset of action, lower dose to produce desired effects and minimal systemic side effects. In mechanically ventilated patients therapeutic agents currently given via inhalation include bronchodilators, corticosteroids, antibiotics, prostaglandins and surfactant. Many barriers were previously thought to preclude effective aerosol therapy in the mechanically ventilated patient. The poor efficiency of aerosol delivery to the lung was a substantial drawback. A complex array of *factors influence aerosol delivery during mechanical ventilation* including variables related to the nebulizer, the ventilator, the ventilator circuit and artificial airway, the inhaled drug or agent, and the patient. Access to distal airways is a function of *particle size* (60, 61). The majority of drug particles in nebulizer aerosols are in the range of 1 – 5 μm. During mechanical ventilation larger aerosol particles are trapped in the ventilator circuit and ETT. In humans, large particles (> 4 μm) and small particles (0.5 to 1.0μm) tend to deposit in the nasopharyngeal structures, whereas intermediate particles (1 to 4 μm) reach distal airways. Both *jet and ultrasonic nebulizers* are employed for delivering aerosols to mechanically ventilated patients (60). Conventional ultrasonic nebulizers produce an increase in the temperature of the solution during nebulization. In addition, the particle size distribution of the aerosols produced by ultrasonic nebulizers in ventilator circuits has not been well characterized. Nebulizers are *connected in the inspiratory limb of the ventilator circuit* or at the patient Y-piece (60). Placing the jet nebulizer at a distance from the ETT offers better efficiency than placing it between the patient Y-piece and the ETT, because the ventilator circuit serves as a spacer for the aerosol to accumulate between inspirations. The efficiency of aerosol generation differs markedly among different *nebulizer brands* (60). Factors that influence nebulizer efficiency are the diluent volume, operating pressure and flow, and duration of treatment. Within the limits of a particular nebulizer design, the higher the gas pressure and/or *flow to the nebulizer*, the smaller the particle size generated. In contrast, the nebulizer with the lowest gas flow through the ventilator consistently delivers the most aerosol to the subject (62). Drug delivery from a nebulizer is significantly reduced by *humidity in the ventilator circuit* (60). Circuit humidity increases the size of aerosol particles and increases particle-impaction losses. Although circuit humidity reduces drug delivery, bypassing the humidifier is not recommended for routine inhalation therapy in mechanically ventilated patients as inhaling dry gas for extended periods could be detrimental to the tracheal mucosa. Moreover, with careful attention to the administration technique the impact of humidity on drug delivery can be overcome by delivering a somewhat higher dose. In a ventilator circuit a nebulizer can be *operated continuously or intermittently* by airflow from the ventilator. Continuous nebulization is the least efficient delivery method (63). Although breath-actuated or intermittent nebulization is preferable, the properties of the aerosol generated and optimal techniques for intermittent nebulization are not well understood. The aerosol-delivery efficiency of the jet nebulizer is influenced by *ventilator-related factors* such as type of ventilation

(volume control associated with greater nebulizer efficiency than pressure control), inspiratory time, inspiratory flow pattern, and lung mechanics (60). _Aerosol impaction in the ETT_ reduces lower airway delivery, particularly in pediatric ventilator circuits (60). When the nebulizer is placed at a distance from the ETT instead of being directly connected to it, drug losses in the ETT are minimized and pulmonary deposition is increased. In adults, pulmonary deposition of aerosol particles ranges from 8 to 22 % (62). _Infants_ have a low tidal volume, vital capacity, and functional residual capacity, and short respiratory cycles (low I:E ratio), which results in low residence time for aerosol particles and, thus, low pulmonary deposition of aerosol particles compared to adults. With improvements in technology and better understanding of the principles of aerosol delivery many of the obstacles to efficient aerosol delivery during mechanical ventilation have been overcome (60).

Efficiency of the MiniHEART nebulizer in drug delivery

The MiniHEART nebulizer is a low flow jet nebulizer that has been shown to be ideal for use in-line with mechanical ventilators and is used in the NICU for continuous nebulization of albuterol and other medications in the newborn. The MiniHEART nebulizer delivers an aerosol particle size of 2-3 μm that is optimal for peripheral deposition in the lung. Studies using the MiniHEART low flow jet nebulizer have demonstrated an _efficiency of 10-14%._

The effectiveness of the MiniHEART nebulizer for administration of nebulized PGI_2 was evaluated in 11 patients with ARDS. Although there was significant improvement in oxygenation, there was no difference in PEEP, mean airway pressure or FiO_2, before and after aerosolized PGI_2. The inhaled aerosol particles had a mass median diameter of 3.1 μm. Emitted dose was 67±13% of the calculated or nominal dose. The average inhaled dose was 14% of the nominal dose and 21% of the average emitted dose. The mean duration of treatment was 41 hrs (range 9 to 116 hrs)(64).

Efficiency of the MiniHEART nebulizer in drug delivery in neonates

After comparison of four nebulizers in administering surfactant in newborn babies, Dijk et al., 1997 (65), concluded that the _low flow nebulizer is the most suitable nebulizer in a neonatal ventilator_ setting because it does not influence airway pressure, has the highest efficiency, produces an aerosol with a good particle size distribution which ensures peripheral deposition in the lungs and does not alter either the composition nor biophysical properties of the surfactant. Using 99m-technetium Nanocoll labeled surfactant dissolved in normal saline in an animal model, they estimated that most of the surfactant aerosol was deposited in the expiratory hose (28%) and the nebulizer (20%). Almost 20% of the surfactant was deposited in the lungs of the rabbit. They demonstrated a higher efficiency of the nebulizer in the animal setting compared to the test lung setting and attributed it to three reasons – higher tidal volume, branching structure of the airways, and gravitational flow of condensed surfactant into lungs in the animal setting.

Efficiency of the MiniHEART nebulizer in drug delivery during high frequency ventilation

Dijk et al., 1998 (66), were the first to report the use of aerosol therapy using a low flow jet nebulizer (MiniHEART) _during high frequency ventilation_ to administer surfactant in rabbits. Surfactant distribution in the lungs was assessed using technetium-99m-labeled Nanocoll. Surfactant deposition after nebulization was 9.8%. It was interesting that the efficiency of nebulization during HFV was almost equal to the efficiency of nebulization during conventional ventilation that the investigators found under equal conditions in the same animal model.

4.0 RESEARCH DESIGN AND METHODS

4.1 Trial Design

This is a multicenter, double-blind randomized controlled clinical trial in which infants will be randomly assigned to receive inhaled PGE_1 or placebo. Fifty patients recruited at 9 high volume sites within the NICHD Neonatal Research Network will constitute a pilot sample to evaluate the feasibility and safety of prolonged $IPGE_1$ administration and determination of optimal dose. In this Pilot RCT, two doses of $IPGE_1$ (300 and 150 ng/kg/min) will be administered over a maximum duration of 72 hours to determine the optimal dose and duration of therapy.

Two initial doses of $IPGE_1$ will be tested – 150 and 300 ng/kg/min. Thus, there will be three arms to the study – $IPGE_1$ [150], $IPGE_1$ [300], and Control. This design will allow comparison of the two doses of $IPGE_1$ with each other and controls; and also allow comparison of any $IPGE_1$ with controls. The two doses of $IPGE_1$ have been selected on the basis of the results of the Phase I/II open label study of $IPGE_1$ in neonatal HRF (67).

4.1.1 Inclusion Criteria

1. Gestational age ≥ 34 weeks and ≤ 7 days (168 hours) postnatal age.
2. Assisted ventilation for hypoxic ventilatory failure.
3. Diagnosis of HRF including perinatal aspiration syndrome (meconium, blood, or amniotic fluid), pneumonia/sepsis, respiratory distress syndrome or idiopathic.
4. An Oxygenation Index (MAP x FiO_2 x 100 / P_aO_2) (OI) ≥ 15 and < 25 on two arterial gases at least 15 minutes apart and no more than 12 hours apart.
5. An indwelling arterial line.
6. Parental consent.

4.1.2 Exclusion criteria

1. Any infant in whom a decision has been made not to provide full treatment (e.g. chromosomal anomalies, severe birth asphyxia).
2. Known structural congenital heart disease except patent ductus arteriosus and atrial/ventricular level shunts.
3. Congenital diaphragmatic hernia.
4. Preterm neonates (< 34 weeks).
5. Thrombocytopenia (platelet count < 80,000/μl) unresponsive to platelet transfusion.
6. Previous treatment with inhaled nitric oxide.
7. Enrollment in a conflicting and/or Investigational New Drug (IND) clinical trial.

4.1.3 Oxygenation Index as a Clinical Indicator of Disease Severity

The arterial-alveolar O2 tension ratio (P_aO_2/P_AO_2, a/A ratio), the alveolar-arterial O_2 gradient or difference ($P_AO_2 - P_aO_2$), the oxygenation ratio, and the Oxygenation index are useful derivatives of blood gas data that serve as clinical indicators of disease severity and may thus function as criteria for judging treatment failure or instituting more invasive forms of therapy.

The alveolar-arterial O_2 gradient ($AaDO_2$) ($P_AO_2 - P_aO_2$) quantifies the O_2 tension gradient between alveoli and blood, and thereby reflects the level of gas exchange through the lungs. A value > 250 mmHg is an indicator of respiratory failure and the need for assisted ventilation. A value > 600 mmHg is a selection criteria for neonatal ECMO

The Oxygenation Index (MAP x FiO_2 x 100/ Postductal P_aO_2) factors in the pressure cost of achieving a certain level of postductal oxygenation and proves useful when the decision to pursue a

different or more invasive or experimental therapeutic modality must be made. A value of > 15 signifies severe respiratory compromise, a value of 30 – 35 suggests failure to respond to existing mode of ventilatory support and a value of ≥ 40 indicates mortality risk approaching 80%, justifying the use of ECMO.

Mean Airway Pressure (MAP, or Paw) is the mean or average pressure transmitted to the airways. It is derived from the equation: MAP = k (PIP – PEEP) [IT / (IT + ET] + PEEP, Where k is a constant that depends on the rate of inspiratory pressure increase, and ET is the expiratory time. In clinical situations, k is always less than 1. A very high MAP may cause over-distension of airways and alveoli, leading to an increase in dead space and right-to-left shunting of blood in the lungs; and decreased cardiac output secondary to decreased venous return and increased PVR, and thus, despite an adequate P_aO_2 and oxygen content, oxygen transport (arterial oxygen content x cardiac output) may decrease.

Current FDA guidelines recommend the use of INO at a persistent OI of ≥ 25. Starting aerosolized PGE_1 at an OI of 15 will select sick patients with HRF justifying the use of this potentially efficacious and safe selective pulmonary vasodilator with the option of giving INO as rescue therapy if the patient continues to deteriorate.

4.1.4 Rationale for an OI of 15 to start study aerosol

The effectiveness of INO in improving oxygenation and reducing the need for ECMO in patients with severe neonatal HRF is well established (1, 3). Most studies to date have enrolled with severe HRF defined as an OI ≥ 25 or an AaDO2 > 600 Torr. Patients with severe HRF are critically ill and on maximal medical support, which in itself may have detrimental effects. It is possible that earlier initiation of therapy may halt the progression to severe HRF and thereby have a positive influence on outcome variables. Data from control arm of studies using early INO suggest that ~60% of babies with OI > 15 progress to OI ≥25 (68-72). These infants may have a window of opportunity to resolve their pulmonary hypertension with early INO before a rapid deterioration in oxygenation occurs, necessitating more invasive therapies and need for transfer to an institution with INO and ECMO capabilities. Lotze et al demonstrated decreased need for ECMO which was greatest for the subgroup with OI 15-22 in response to administration of surfactant for babies with HRF (69). Sadiq et al (2003) showed in a randomized controlled study that INO in patients with moderate pulmonary hypertension improves P_aO_2, reduces the amount of ventilatory support needed, and prevents progression to severe HRF (68). Three other studies have reported the use of INO use in moderate or early HRF (70-72). Davidson et al demonstrated an acute and sustained improvement in oxygenation for 24 hours in a majority of term infants with early but moderately severe HRF (70). Furthermore, oxygenation appeared to be stabilized to a greater degree by INO whether the patient became a treatment success or failure. There was a suggestion that ECMO was reduced by 35%. The Franco-Belgian Collaborative NO trial group included near-term infants with OI between 15 and 40 (71). They reported a lower OI at 2 hours and a shorter duration of mechanical ventilation (6 vs 7 days) in INO treated infants compared to control infants. Konduri et al conducted a randomized, double masked, multi-center trial of early treatment with INO in term/near term infants with respiratory failure (72). 73% of EINO infants had an increase in P_aO_2 > 20 torr at study gas initiation compared to 37% of controls ($p<0.001$). Control infants progressed to standard INO and to OI > 40 more often ($p<0.05$) than EINO infants.

Although existing literature suggests that earlier treatment of respiratory failure may halt the progression to severe HRF, on the other hand, it is possible that patients with early or moderate HRF may have only a moderate degree of pulmonary vasoconstriction, and improvement in oxygenation with earlier therapy might be less than that seen with severe HRF (68). Furthermore, as all studies in neonates with moderately severe HRF were underpowered to demonstrate statistically significant improvements in the primary outcome endpoint of ECMO/death (68, 70, 72, 73), there may be lack of efficacy or failure to recruit adequate number of subjects in the proposed study.

4.1.5 Informed consent

Informed parental consent will be obtained. The consent form will be specifically designed to address the phase III randomized clinical trial of aerosolized PGE_I in a baby with an OI of ≥ 15. Consent will also specify that during the study the infant will continue to receive "standard of care" treatment as determined by the treating physician.

4.2 Methods

4.2.1 Assignment to Treatment Groups

Eligible infants will be randomly assigned to either $IPGE_I$ [150], $IPGE_I$ [300] or control group. Infants in the control group will receive aerosolized saline and oxygen from the respirator as before.

4.2.2 Stratification

Randomization will be stratified by clinical center. This pre-stratification is to minimize the potential imbalance between the treatment groups with respect to the anticipated differences in the patient populations and possible differences in patient management.

4.2.3 Randomization

Eligible infants will be randomized using block randomization stratified by center to maintain balance between the number of participants in each group. The infant will be allocated to either low dose PGE_I (150 ng/kg/min), high dose PGE_I (300 ng/kg/min), or control group by random assignment using a randomization list. The randomization list will be kept in the pharmacy or research office at each site and only pharmacy staff or the research staff will have access to the list at each site. The medication will be reconstituted by the pharmacist/research nurse for delivery to the eligible infants. Placebo will consist of aerosolized saline.

4.2.4 Level of Masking

The $IPGE_I$ will be double masked – neither the parents nor the infants' caregivers will be aware of the treatment assignment, with the exception of the pharmacist/research nurse. The infant will be allocated to either low dose PGE_I (150 ng/kg/min), high dose PGE_I (300 ng/kg/min), or control group by random assignment stratified by center. Only one individual from each participating center (either the pharmacist, or research staff), will be aware of the infants' assigned group. PGE_I is colorless and odorless and will therefore be indistinguishable from the placebo. Consequently, all caregivers will remain blinded to treatment group. If assigned the active medication i.e., PGE_I, the pharmacist will reconstitute PGE_I in normal saline in a syringe to deliver either 300 or 150 ng/kg/min of PGE_I in a volume of 2 ml/hour according to a previously designed dose algorithm. If assigned to placebo, an equal volume of normal saline will be drawn up in a similar syringe to be delivered at a rate of 2 ml/hr. The study medication will be reconstituted in the pharmacy. The reconstituted active medication is colorless, odorless, and tastes like normal saline; therefore, there is no danger of unmasking by the physical characteristics of the reconstituted study medication.

Unblinding:
Blinding will be maintained to the extent possible In the event unblinding deemed necessary, the site Principal Investigator will discuss the potential for unblinding with the study Principal Investigator who will make the decision to allow unmasking of treatment assignment.

4.2.5 Screening procedure

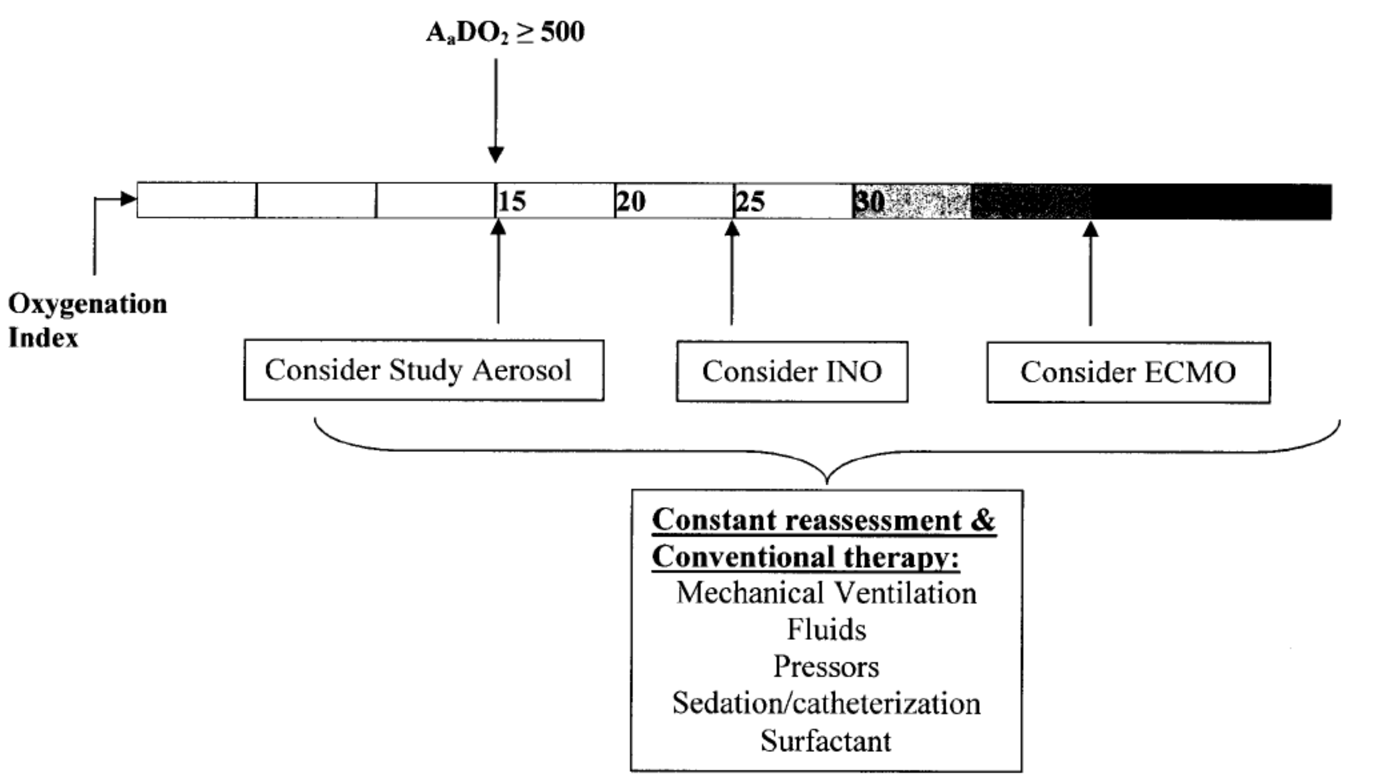
All infants who are ≥ 34 weeks gestation requiring ventilator support will be screened for entry into the study by a research nurse.

4.2.6 Patient Management Protocols

Conventional management will be optimized prior to randomization and treatment with study aerosol. Guidelines for the use of surfactant, conventional or high frequency ventilation and use of hyperventilation and alkali infusion will be defined to standardize their use as far as possible. Prior to initiating the pilot RCT, a consensus management plan will be developed among and within the participating sites. A survey will be sent to the participating centers to determine the practices in the management of PPHN / HRF.

Arterial blood gas (ABG) analysis will be performed 60±15 minutes after study aerosol initiation. Infants who fail to show a response on this ABG will continue on study aerosol and have a subsequent ABG drawn 4±2 hours later. Infants demonstrating a response to study aerosol will continue to receive study aerosol and have ABG's drawn every 12±2 hours and as clinically indicated. After the initial 60±15 min observation period, therapeutic decisions will be left to the clinical team.

An attempt will be made to obtain a cardiac echocardiogram prior to starting study medication to document presence of pulmonary hypertension and assess myocardial function and after discontinuation of study medication as clinically indicated. In patients in whom an echocardiogram is obtained after discontinuation of study medication, changes from initial echocardiogram and ductal patency will be assessed. A cardiac echocardiogram is not a requirement for enrollment in this study as previous studies have shown a lack of correlation between echocardiographic indices of pulmonary hypertension and response to selective pulmonary vasodilators like INO. This is because selective pulmonary vasodilators improve the matching of ventilation with perfusion thus reducing intrapulmonary shunting even in the absence of intra-cardiac shunts (1, 74-76). Roze et al., documented improvement in oxygenation after administration of INO in 17 newborns with severe hypoxemia with or without the presence of right-to-left extra-pulmonary shunt (77). Similarly, in 50 newborns with respiratory failure and pulmonary hypertension, there was no correlation between the baseline ductal shunt and change in oxygen tension and only a weak correlation between the change in ductal shunt and the change in oxygen tension following INO (78). In the NINOS trial, 78% of 226 infants had echocardiographic evidence of pulmonary hypertension (1, 79). Posthoc subgroup analysis did not show a significant difference in outcome related to echocardiographic evidence of pulmonary hypertension.



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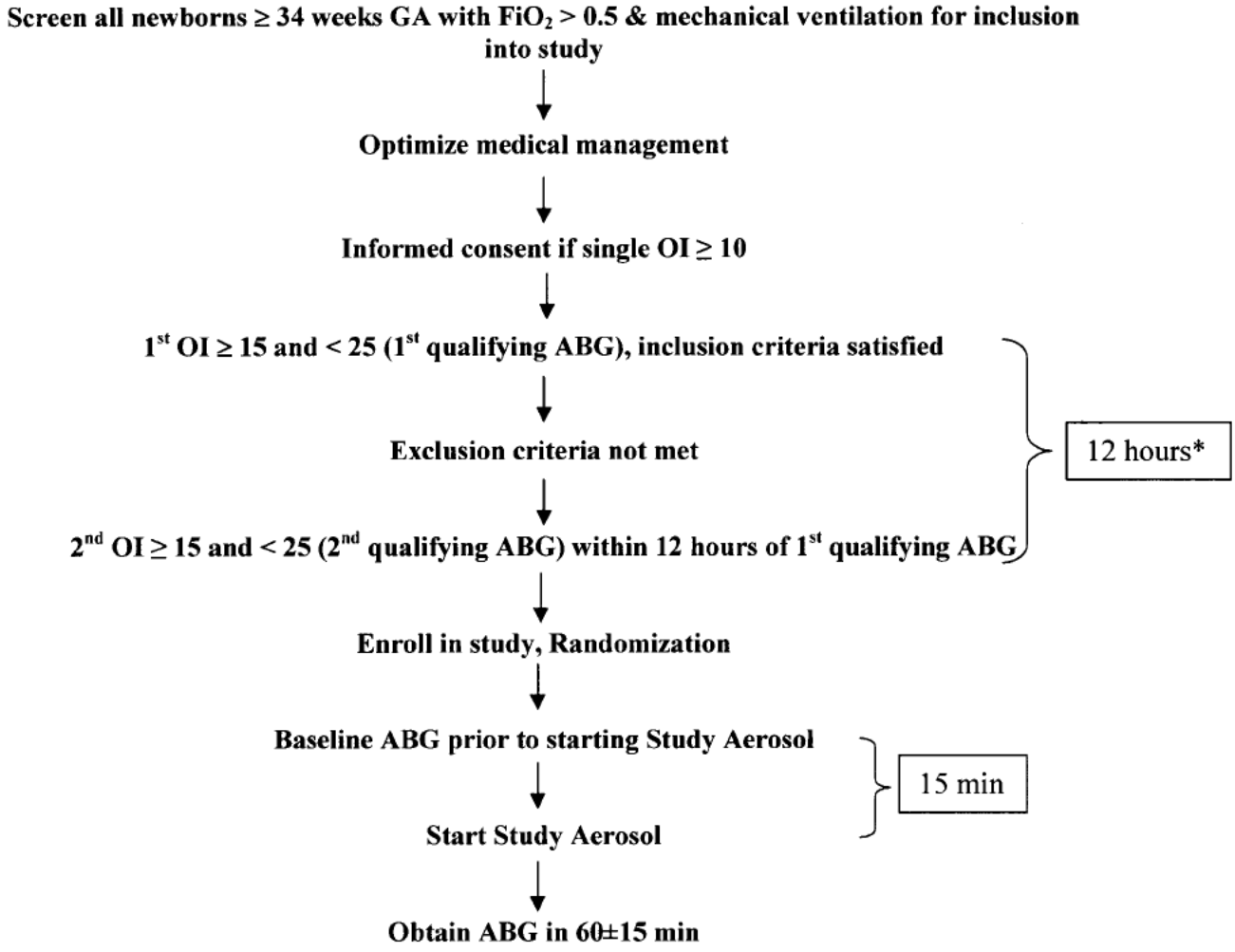
5.0 ADMINISTRATION OF STUDY AEROSOL

5.1 Screening procedure

All infants who are ≥ 34 weeks gestation requiring ventilator support will be screened for entry into the study by a research nurse.



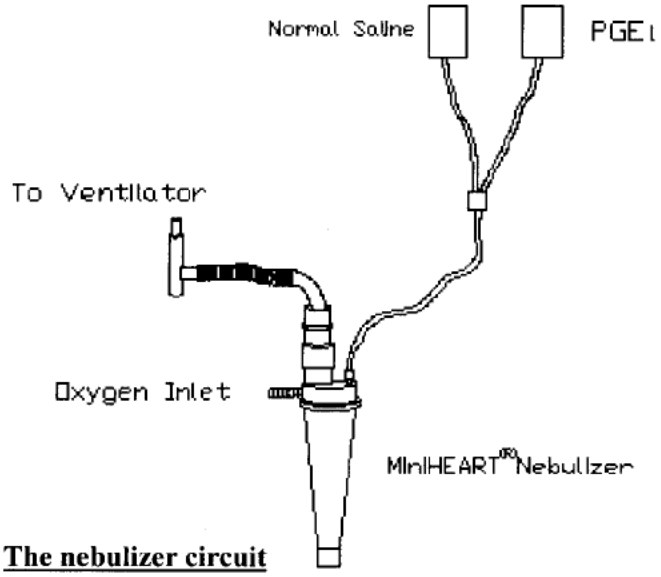
* The two qualifying gases need not be contiguous but have to occur within a 12 hour period.

5.2 Randomization

Parents of all infants screened for entry into the study will be approached for consent for enrollment to the study if the infant has a single OI $\geq$ 10. If an eligible infant has an arterial blood gas (ABG) with an OI in the qualifying range (1st Qualifying gas) after optimizing medical management, preparations to administer study drug will be initiated. This includes having a nebulizer set up ready by the patient's bedside. If a second ABG obtained at least 15 minutes, and no more than 12 hours, after the initial ABG also has an OI in the qualifying range (2nd qualifying gas), the infant will be allocated to either low dose PGE_1 (150 ng/kg/min), high dose PGE_1 (300 ng/kg/min), or control group by random assignment stratified by center. Only one individual from each participating center (either the pharmacist or research nurse,), will be aware of the infants' assigned group. PGE_1 is colorless and odorless and will therefore be indistinguishable from the placebo. Consequently, all caregivers will remain blinded to treatment group. The nebulizer will be set up inline with the patient's ventilator circuit. Study aerosol should be administered immediately after the randomization call is made and within 15 minutes of the last qualifying gas. If it is not possible to start the study aerosol within 15 minutes of the second ABG, a further ABG will be obtained prior to study drug initiation. The ABG obtained 15 min prior to starting the study drug will be considered the baseline ABG (Baseline ABG). Study drug will be administered regardless of the calculated OI on the baseline ABG.

5.3 Drug Dosing

Eligible infants will receive continuous aerosolized PGE_1 or saline. PGE_1 will be obtained by the pharmacy at each participating center in accordance with current practice. Each pharmacy will maintain a drug accountability form including details of lot# and PGE_1 usage. PGE_1 solution will be prepared from synthetic PGE_1 (500 µg dissolved in 1 ml ethanol) by dilution in preservative free sterile 0.9% saline. Fresh solutions will be prepared every 24 hours. The study medication will be delivered using a syringe pump into the nebulizer chamber through a stopcock. The nebulizer chamber will be primed with 2 ml of study medication at the time of study aerosol initiation. For weaning purposes, normal saline will be administered using a second syringe pump with a Y-connection into the nebulizer chamber such that the total volume delivered equals 2 ml/hour. Aerosols of PGE_1 with a mean particle size of 2 to 3 µm will be generated with a jet nebulizer. The nebulizer will be connected to the inspiratory limb of the ventilator (Figure 3). Neonates will be managed with time-cycled, pressure-limited ventilators or high frequency oscillators. During the inhalation period, the ventilator tidal volume and the FiO_2 will be adapted according the additional oxygen flow of the nebulizer to maintain alveolar ventilation and inspired oxygen concentration. Aerosol application will begin with a PGE_1 dosage of either 300 or 150 ng/kg/min diluted in 2 ml preservative free sterile normal saline/hr in study patients and 2 ml preservative free sterile normal saline/hr in control patients. This PGE_1 dosage refers to the total amount of nebulized drug; its deposition fraction in the lung of each individual patient will not be assessed. The aerosol fraction deposited in the alveolar space during mechanical ventilation is estimated to be less than 10 to 20% (Walmrath, 1996). The alveolar dose is even smaller in newborn infants as there is a proportionally



The nebulizer circuit

larger dead space (Bindl, 1994). Hemodynamics and gas exchange (arterial blood gas) will then be assessed before and 60±15 min after onset of study drug aerosolization. Any change in need for support with inotropes and mechanical ventilation will be recorded during the entire period of investigation.

5.4 Monitoring of Study Aerosol administration

Infants will be clinically monitored for fever, hypotension, tachycardia, arrhythmias, diarrhea and seizures.

5.5 Masking & Safety

The clinical team, nursing staff, respiratory therapists and parents of patients will all be blinded to the study drug. The only unblinded individual is the pharmacist/ research nurse who will determine the treatment group assignment after randomization and reconstitute the study drug for nebulization.

5.6 Response to study medication

An ABG will be obtained 60±15 min after starting the study aerosol unless clinically indicated before then. A positive response will be defined on the basis of an increase in P_aO_2 above baseline after 60±15 min exposure to study aerosol:

Full response: $\geq$ 20 mmHg increase in P_aO_2
Partial response: 10-20 mmHg increase in P_aO_2
No response: < 10 mmHg increase in P_aO_2

The infant will be continued on the study aerosol even if the P_aO_2 does not show an initial improvement (60±15 min) after initiation of study aerosol as previous studies with INO have shown delayed response in a proportion of patients. An ABG will be obtained after 4±2 hours of study aerosol administration or earlier if the baby is determined to be eligible for treatment with INO prior to the completion of the 4±2 hour window. Study aerosol will be discontinued if this ABG demonstrates lack of response to study aerosol administration. Lack of response for this ABG will be defined as an increase in OI of $\geq$ 5 compared to the baseline ABG or an absolute OI $\geq$ 25.

5.7 Outcome Variables

5.7.1 Primary Outcome

1. The primary outcome is the ability to recruit adequate number of patients in a 6-9 month period without excessive (>20%) protocol violations.

5.7.2 Secondary Outcomes

1 Progression to an OI $\geq$ 25
2 Improvement in PaO_2
2. Change in OI
3. Death
4. Need for INO, ECMO
5. Length of hospitalization
6. Duration of mechanical ventilation
7. Number of days of O2 used, and need for supplemental O2 at 28 days of life.
8. Occurrence of grade III-IV intracranial hemorrhage, and cystic leukomalacia

5.8 Treatment Failure Criteria

Treatment failure criteria have been chosen to allow sufficient time for high frequency oscillatory ventilation, INO, and to prevent delay in beginning ECMO in those infants with severe hypoxemia (80).

5.8.1 Deterioration on Initiation of Study Aerosol

If, upon the initiation of study aerosol, there is an acute deterioration in clinical status (absolute fall in pulse oximeter O_2 saturation by > 10%), before the 60±15 minute waiting period for assessment has passed, study aerosol will be discontinued and the infant will be assessed to confirm worsening oxygenation and to rule out causes such as pneumothorax or plugged/mal-positioned ETT. Once the patient has been stabilized, study aerosol administration will be repeated using the initial dose of 2ml/hr.

If there is an acute deterioration or requirement for intervention with the second attempt to initiate study aerosol, an ABG should be drawn, and if the deterioration is not due to an identifiable mechanical problem, study aerosol will be discontinued, and the patient classified as a study drug non-responder. These infants will receive INO and/or ECMO as is standard of care.

5.8.2 Deterioration during Administration of Study Aerosol

If at any time during the administration of study aerosol there is an acute deterioration in clinical status (absolute fall in pulse oximeter O_2 saturation by > 10%), study aerosol will be discontinued after ruling out mechanical causes such as pneumothorax or plugged/mal-positioned ETT for the deterioration.

5.8.3 Criteria for starting Standard INO

It is recommended that treatment be initiated with INO if an OI ≥ 25 is documented on 2 consecutive ABGs at least 15 minutes apart.

Infants who have shown a positive response to study aerosol at 60 + 15 minutes or 4+2 hrs after study aerosol initiation will continue to receive study aerosol even if the infant meets criteria for Standard INO.

The maximum duration of study aerosol will be 72 hours.

5.8.4 Criteria for ECMO

Criteria for ECMO will be agreed upon by the participating sites prior to initiation of the multi-center pilot RCT. In addition, site specific criteria for ECMO will be followed. In general, any baby with an oxygenation index > 40, or an alveolar arterial PaO2 gradient > 620 for 8 hours or a PaO2 < 40-50 acutely will be considered for ECMO.

5.9 Weaning of Study Aerosol

After prolonged NO administration, endogenous NO production is inhibited and therefore the NO has to be weaned very slowly. Similar decrease in P_aO_2 after withdrawal has not yet been reported after inhaled PGE_1 use in experimental or human newborn studies. However, it is proposed to wean the aerosolized PGE_1 gradually in 12 hr steps to avoid the potential drop in P_aO_2.

For any given weaning time point, weaning will be attempted only if the P_aO_2 is > 60 torr. The first weaning attempt will be at 12±2 hours. Further weaning attempts will be mandated at 12±2 hr intervals. In addition to the regularly scheduled weaning attempts, additional weaning attempts may be made if the OI < 10 on a single ABG. Repeated weaning attempts should not be made within 2 hours of a

wean. For each wean attempt, a baseline ABG will be drawn, the study aerosol weaned by 50%, and an ABG drawn 60±15 min later. The FiO_2 and ventilator settings will not be changed during the weaning attempt. The FiO_2 and ventilator settings may be adjusted at all other times at the discretion of the clinical team. The wean attempt will be considered successful if the decrease in P_aO_2 is ≤ 35% and the post-wean P_aO_2 remains > 60 mmHg. If the arterial line is no longer present, pre-wean SpO2 should be > 95% to attempt weaning and the post-wean SaO_2 should be > 95% for wean to be considered successful. Sequential weaning steps involve weaning of study aerosol dose by 50% at each wean followed by discontinuation at the fourth wean. This will be achieved by increasing the amount of saline nebulized while maintaining a nebulizer output of 2 ml/hr. If following a weaning attempt, the decrease in P_aO_2 is > 35% and the post-wean P_aO_2 is < 60 mmHg, the dose of study aerosol will be escalated to the immediate pre-wean dose. The total duration of study aerosol administration should not exceed 72 hours. Wean to the 3rd dose should be accomplished by 48 hours on study aerosol.

	Study Medication (ml/hr)		**Normal Saline (ml/hr)**		**Total rate (ml/hr)**	
	2	+	0	=	2	**DOSE 1**
Wean 1	↓		↓		↓	
	1	+	1	=	2	**DOSE 2**
Wean 2	↓		↓		↓	
	0.5	+	1.5	=	2	**DOSE 3**
Wean 3	↓		↓		↓	
	0.25	+	1.75	=	2	**DOSE 4**
Wean 4	↓		↓		↓	
	OFF	+	**OFF**	=	**OFF**	

5.10 Weaning of ventilator during study

Guidelines for weaning from mechanical ventilation for both groups will be determined by the participating sites prior to embarking upon the multi-center pilot RCT.

5.11 Maximal Duration of Study Aerosol

Study aerosol administration must be terminated at 72 hrs (3 days).

5.12 Study Drug Discontinuation

Study drug will be discontinued whenever weaning has been successfully accomplished at either the regularly scheduled wean or after a weaning attempt allowed by one ABG when the OI < 10. The maximal duration of study drug administration will be 72 hours (3 days).

5.13 Criteria for Study Aerosol Re-initiation

Study drug will not be re-initiated after a successful wean.

5.14 Toxic Effects

Clinical monitoring for hyperthermia (> 38° c), bradycardia (HR < 70) arrhythmia, hypotension, seizures, bleeding tendency, pulmonary hemorrhage, diarrhea and seizures, will be done continuously throughout the study. Study aerosol will be weaned if hypotension or arrhythmia persists despite maximal therapy.

During the trial, response variables will be monitored for early dramatic benefits or potential harmful effects by a group independent of the principal investigators. A Data Safety Monitoring committee will review all the data from the Study. Blinding will be maintained but the adverse events between groups will be compared. Should there be an excess adverse event in one group the committee may recommend breaking of the blinding and or discontinuation of the study.

Efforts to obtain an autopsy will be made for every study infant that expires.

6.0 SAMPLE SIZE

6.1 The Pilot RCT

The pilot RCT is primarily designed to evaluate the feasibility and safety of prolonged $IPGE_1$ administration and determination of optimal dose in 50 patients recruited at the high volume sites within the NICHD Neonatal Research Network. The participating sites (PIs) for the Pilot RCT trial are: Alabama (Wally Carlo), Florida (Shahnaz Duara), California (Neil Finer), Indiana (Greg Sokol), Detroit (Seetha Shankaran), Cincinnati (Ed Donovan), Stanford (Krisa Van Meurs), Duke (Ronald Goldberg) and Case Western (Michele Walsh). We queried five of these sites regarding the number of neonates admitted with a diagnosis of HRF requiring treatment with INO in Dec 2004. In ~ 11 months (Jan to Dec 2004), a total of 164 patients received INO at the 5 Pilot sites. Of these, 23.8% received transport INO. There was variability in sites in the use of transport INO. However, overall there were 125 patients in the 5 sites who were admitted without transport INO. A significant number of these would be potential candidates for the $IPGE_1$ Pilot. Therefore we hope to complete enrollment in the pilot RCT in a period of 6 - 9 months. If a site does not enroll subjects within 3 months, the PGE_1 Subcommittee may recommend that the site not participate in the pilot.

a. Ability to recruit 50 patients over a 6 – 9 month time period: To enhance patient recruitment, consent from the families will be sought once an infant has one OI $\geq$ 10, in readiness for randomization when the patient has 2 qualifying gases within a 12-hr period [i.e., OI $\geq$ 15 and 25].
b. Lack of serious adverse effects
c. Some evidence of efficacy: Relative risk of 67% (range 50 – 80%) for treatment compared to control arm for progression of OI to $\geq$ 25. We will not look for statistical significance in the Pilot trial because it is not powered to detect statistically significant differences in outcomes. (In other words, we expect that the 95% confidence limits for our relative risk estimate of 0.67 will include 1.) Additional comparisons between the groups will be made on the basis of clinical relevance of the treatment differences within the constraints of limited sample size

We did not consider decrease in mortality as an outcome as it has previously been demonstrated that when ECMO is offered as a treatment of last option following failure of response to combination of treatments, the mortality rate is reduced to 11% (45). RCT studies with INO have shown that the use of INO has decreased the rate of ECMO utilization but the mortality is unchanged (1, 3). Therefore, studies that evaluate therapies for HRF together with ECMO must use outcome measures other than mortality to assess the efficacy of these treatments (45).

7.0 DATA ANALYSES AND STATISTICS

Data will be collected during the administration of inhaled PGE_1 and will include arterial blood gas parameters and hemodynamic variables. Additionally, the patients' medical record will be abstracted by the research nurse/principal investigator for relevant perinatal and postnatal variables for entry into a computerized database. A sample data collection form that was used for the pilot study has been attached.

Data will be presented as mean ± SD for normally distributed variables and as median and ranges (with percentiles) for non-normally distributed data. All analysis will be by intention-to-treat. Chi-square and Fisher's exact test will be used to compare discrete variables and continuous variables will be compared using *t*-test and ANOVA. Longitudinal data will be analyzed using the mixed procedure in SAS. Nonparametric Kaplan-Meier curves will be plotted depicting proportion of responders versus survival time in hours. The analysis will account for stratification by clinical site. The potential influence of baseline measures on the outcome will be measured through the use of logistic regression models.

Additional analysis, including summaries of the results in pre-defined subgroups, will be presented for the primary study outcome and for the probability of reaching an OI of 25 and OI of 40. The subgroups will be based on primary diagnosis, presence/absence of echocardiographic pulmonary hypertension, treatment with surfactant, use of high frequency ventilation (HFV), combined treatment with surfactant and HFV, and P_aO_2 response to study aerosol. Analyses for the secondary hypotheses will be based on appropriate statistical tests depending on the type of outcome (e.g., analysis of covariance, two-sample *t*- or Wilcoxon tests).

8.0 SAFETY MONITORING

The following measures will be used to monitor safety of the trial.

1. The protocol will be reviewed by the Institutional Review Board of each participating institution.
2. Adverse event reporting will be handled as follows: all adverse events will be reported on the MedWatch form to the Data Center. Serious adverse events occur (as defined below) they will be reported on the Serious Adverse Events form. These events include: (a) hypotension, (b) cardiac arrhythmia, (c) seizures, (d) bleeding, (e) diarrhea, (f) elevated temperature/fever and (g) death. A composite adverse event measure made up of these serious adverse events will be derived.
3. All protocol deviations will be monitored.
4. The Data Safety Monitoring Committee (DSMC), consisting of three Neonatologists, an Obstetrician, an Epidemiologist, and a Statistician, will be responsible for monitoring the safety of the trial. The DSMC will review all the data from the study at the conclusion of the Pilot RCT unless required to do so earlier by RTI because of safety concerns. Blinding will be maintained but the adverse events between groups will be compared. Should there be an excess adverse event in one group the committee may recommend breaking of the blinding and or discontinuation of the study.

APPENDIX I

Studies of Inhaled Prostaglandins in Pulmonary Hypertension - Animals

Author, yr Patient	Drug	Outcome measures	Side effects
Welte, 1993 6 dogs	$IPGI_2$, INO	↓ PAP, $IPGI_2$ less potent	None
Zobel, 1995 12 piglets	$IPGI_2$, i.v. PGI_2, iNO	Oxygenation and pulmonary hemodynamics improved with all	MAP ↓ – i.v. PGI_2
Booke, 1996 6 ewes	$IPGI_2$, INO	Selective pulmonary vasodilation.	
Habler, 1996 14 Healthy lambs	$IPGI_2$		None
Habler, 1996 15 healthy lambs	$IPGI_2$		None
Walmrath, 1997 Rabbit lung	INO, $IPGI_2$, $IPGE_1$, i.v PGI_2, i.v PGE_1	Inhaled agents comparable i.v PGI_2/PGE_1 not effective	
Krieg, 1998 24 pigs,	INO, $IPGE_1$, INO + $IPGE_1$		INO significantly reduced left ventricular contractility
Ikeda, 1999 Anesthetized cats	INO, $IPGI_2$, INO + $IPGI_2$, $IPGI_2$ after L-NAME, Papaverine 2 mg/kg	INO & $IPGI_2$ dilate 100–900 μm pulmonary arteries in a dose dependent manner Their combination produces a more enhanced vasodilator effect	Effect on SAP: INO – No change $IPGI_2$, INO + $IPGI_2$, Papaverine – decrease

Table 2: Studies of Inhaled Prostaglandins in Pulmonary Hypertension - Humans - Children & Neonates

Author, yr Patient	Drug	Outcome measures	Side effects
Bindl, 1994 2 newborns - PPHN	$IPGI_2$	↑ P_aO_2, ↓Pulmonary BP.	No drop in SBP
Pappert, 1995 Three 8 yr old-ARDS	$IPGI_2$, INO for 30 min	↑ P_aO_2, selective pulmonary vasodilation	No ↓ in SBP with either agent
Santak, 1995 4-month old - PPH	i.v PGI_2, $IPGI_2$ for 20 min	$IPGI_2$ ↓ PAP and PVRI	$IPGI_2$ ↑ CI with hardly any effect on SAP
Zwissler, 1995 Term neonate with CHD	$IPGI_2$, INO 40 ppm	Improved gas exchange, ↓ PAP	SAP unchanged, No bleeding
Soditt, 1997 Preterm, 28 weeks, HMD, PPHN, 34 h	$IPGI_2$	Dramatic improvement in OI	Systemic arterial pressures remained stable, no bleeds
Kelly, 2002 4 term infants refractory to INO	$IPGI_2$, milrinone i.v.	Improvement in oxygenation, ↓ PAP	None
Hsiao, 2004 3 preterm infants, PPHN	$IPGI_2$	Improved oxygenation	None

Table 3: Studies of Inhaled Prostaglandins in Pulmonary Hypertension - Human Adults

Author, yr Patient	Drug	Outcome measures	Side effects
Walmrath, 1993 **ARDS - 3 adults**	$IPGI_2$, i.v. PGI_2	i.v.PGI_2 increased shunt flow	Slight ↓ in mean systemic BP
Bein, 1994 **1 adult**	$IPGI_2$	Rapid improvement in arterial oxygenation and ↓ in mean PAP	HR and SAP unchanged
Walmrath, 1995 **12 adults**	$IPGI_2$	Decrease mean PAP; improved oxygenation	SAP decreased
Bein, 1996 **8 adults**	$IPGI_2$ Exposure period 15 min	↓ PAP, PVRI, improved oxygenation	HR, MBP, CVP, PAWP unchanged.
Eichelbronner, 1996 **16 adult with PHT**	INO $IPGI_2$	Both selectively ↓ mean PAP	$IPGI_2$ improved splanchnic perfusion
Haraldsson, 1996 **9 adults with PHT,**	$IPGI_2$ Exposure period 10 min	Dose dependent selective pulmonary vasodilation	No changes in HR, MAP, PCWP, CO
Olschewski, 1996 **6 adults with PHT**	$IPGI_2$, i.v. PGI_2, INO, Aerosolized iloprost	INO less potent pulmonary vasodilator than $IPGI_2$	$IPGI_2$ - MSAP only slightly affected
Walmrath, 1996 **16 adults - ARDS**	I NO, $IPGI_2$ – for 15 min	↓ in PAP	No effect on SAP and SVR
Webb, 1996 **65 yr, M, PE, PHT**	$IPGI_2$ for 24 hours	↓ PAP, PVRI, ↑ oxygenation	No change in SBP
Van Heerden, 1996 **2 adults**	$IPGI_2$	Marked ↑ in P_aO_2	No systemic hypotension
Van Heerden, 1996 **5 adults with ARDS**	$IPGI_2$, INO Exposure for 30 min	↑ P_aO_2, ↓ PAP	MAP, CO, HR, CVP, PCWP unchanged
Haraldsson, 1998 **10 adults**	$IPGI_2$, INO for 10 min	↓ PAP and PVR	HR, MAP, CVP, SVR unchanged, $IPGI_2$ ↑ CO
O'Hare, 1998 **Pregnant woman**	$IPGI_2$		
Meyer, 1998 **15 adults with ALI**	$IPGE_1$	↑ P_aO_2, ↓ venous admixture, improved pulmonary function	No effect on systemic hemodynamic variables
Putensen, 1998 **10 adults with ARDS**	INO, $IPGE_1$, i.v PGE_1 no intervention	INO and i PGE_1 equally ↓ PVR and improve gas exchange	INO and $IPGE_1$ did not affect SBP or SVR
Olschewski, 1998 **45 yr, F, PHT,**	Aerosolized iloprost INO	Both ↓ PVRI, ↑ P_aO_2	Neither caused change in SBP
Olschewski, 2000 **19 adults with PHT**	Inhaled iloprost	Pulmonary vasodilation	Improved hemodynamics

APPENDIX 2

Budget for $IPGE_1$ Study through NRN – Pilot study for 50 patients

Personnel:		
Principal Investigator (Effort=0.3)		$0.00
Nursing Care in hours (per hour)	$32.00	$19,200.00
Pharmacy:		
Pharmacy start-up fee	$1,100.00	$9,900.00
PGE_1	$48.47	$16,479.80
Respiratory Care Cost:		
Daily continuous nebulization	$100.00	$15,000.00
Central reader for Echos	$50.00	$2,500.00
Total Direct Costs		$63,079.80
Estimated per capita cost		$1,239.60
Available Funds:		
Funding through K23 to BGS		~$40,000
Funding provided by CHM		~$20,000
Total Available Funds		**~$60,000**

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Sample Consent

Parental Permission/Research Informed Consent

Title of Study: **Pilot Randomized Clinical Trial of Inhaled PGE$_1$ in Neonatal Hypoxemic Respiratory Failure**

You and your child are being asked to be in a research study of severe breathing problems (respiratory failure) in term/near-term newborns at Wayne State University. Your child is being asked take part in this study because he/she has severe breathing problems as assessed by blood gases. Please read this form and ask any questions you may have before agreeing to be in the study.

The study is being conducted at Wayne State University by Beena G. Sood, MD, Department of Pediatrics. Her associates at Wayne State University and the National Institute for Child Health and Human Development (NICHD) Neonatal Research Network will also be taking part in this study. The funding for this study is being provided by the National Institute for Child Health and Human Development (NICHD), and the Children's Research Center of Michigan (CRCM). Nebulizers are being provided by Westmed Inc., Tucson, AZ.

Study Purpose:
The purpose of the study is to evaluate the usefulness of a new treatment for severe breathing problems (respiratory failure), inhaled PGE$_1$ (IPGE$_1$) in term and near-term newborns. Respiratory failure is associated with narrowing of blood vessels in the lungs. PGE$_1$ may open up the blood vessels by causing relaxation of smooth muscle in the walls of blood vessels. PGE$_1$ given by vein (intravenously) has been used in respiratory failure in newborns but the results are inconsistent. The drug works on blood vessels in many organs when it is given by vein. Breathing fine particles of PGE$_1$ (inhalation) using a machine that converts PGE$_1$ solution to a fine spray (nebulizer) should deliver the drug directly to the lungs and minimize its action on blood vessels in other parts of the body. The expected number of study participants to be enrolled at Wayne State University is about ten as well as about 40 from eight other participating sites across the United States.

Study Procedures:
If your child takes part in the study, he/she will be treated for a maximum duration of 72 hours (3 days) with either the study medication (IPGE$_1$) or placebo. A placebo is something that looks like the study medication but doesn't contain real medicine. Your child will be assigned by random (like the roll of a dice) to receive one of three treatments being evaluated in this study: high dose IPGE$_1$, low dose IPGE$_1$ or placebo. Your child's chances of being assigned to any of the three treatment groups are equal i.e. one out of three chance of getting any of the treatment options. Neither the clinical nor the research staff will be aware of the treatment your child is assigned to. The study medication or placebo will be administered as a breathing treatment using a nebulizer connected to the ventilator for a maximum of 72 hours (3 days). During the study, your child will continue to receive "standard of care" treatment as determined by the treating physician in addition to the study medication or placebo administered by the research staff. Your child will be monitored during the study as is routine for babies with this condition. As part of the study the research team will be reviewing both your and your child's medical records. If

Sample Consent

funding becomes available, you and your child may be asked to return for a physical examination and tests of development when your child is older. You will be asked to sign an additional consent if you agree to take part in the later testing.

Benefits:
The possible benefits to your child for taking part in this study are improvement in the baby's breathing, and possibly avoiding the need for other therapies. Additionally information from this study may benefit other children with similar health issues now or in the future.

Risks:
By taking part in this study, your child may experience the following risks that have been reported with the PGE$_1$ when it is given intravenous (by vein): low blood pressure (hypotension), fever, convulsions (seizures), irregular hear beat (arrhythmias), bleeding tendency, and diarrhea. Because the medication will be given by breathing treatment (inhalation), these side effects will be even more unlikely. Infants will be closely monitored during the study for the presence of fever, low blood pressure, irregular heart beat, and seizures and should these occur, appropriate treatment will be given. There may also be risks involved in taking part in this study that are not known to researchers at this time.

Alternatives:
If your child does not participate in this study, s/he will continue to receive standard treatment for her / his condition.

Research Related Injuries:
In the event that research-related activity results in an injury, treatment will be available including first aid, emergency treatment and follow-up care as needed. Care for such will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation or free medical care is offered by Wayne State University, National Institute of Child Health, Children's Research Center of Michigan, or Detroit Medical Center. If you think that your child has suffered a research related injury, let the investigator know right away.

Study Costs:
There will be no additional costs to you or your child for participation in this research study.

Compensation:
You or your child will not be paid for taking part in this study.

Confidentiality:
All information collected about you and your child during the course of this study will be kept confidential to the extent permitted by law. You and your child will be identified in the research records by a code name or number. Information that identifies you and your child personally will not be released without your written permission. However, the study sponsor, the Human Investigation Committee (HIC) at Wayne State University or federal agencies with appropriate regulatory oversight, may review your child's records.

Sample Consent

Personal Health Information (PHI) used and disclosed for the purposes of this study is protected under the federal regulation known as HIPAA (Health Insurance Portability and Accountability Act). The study investigator will discuss with you your rights under this federal regulation and obtain your authorization to allow the research team to access your child's PHI.

Voluntary Participation /Withdrawal:
Taking part in this study is voluntary. You may choose to allow your child to take part in the study and later change your mind and withdraw your child from the study. You or your child are free to not answer any questions or withdraw at any time. Your decision will not change any present or future relationships with Wayne State University or its affiliates or other services you or your child are entitled to receive. The investigator, or the sponsor, may stop your child's participation in this study without your consent. While taking part in this study, you will be told of any important new findings that may change your willingness to continue to have your child take part.

Questions:

If you have any questions now or in the future, you may contact Beena G. Sood, MD. MS or one of her research team members at the following phone number 313-745-5638. If you have questions or concerns about you or your child's rights as a research participant, the Chair of the Human Investigation Committee can be contacted at (313) 577-1628.

Sample Consent

Consent to Participate in a Research Study:
To voluntarily agree to have your child take part in this study, you must sign on the line below. If you choose to have your child take part in this study, you may decide to withdraw him/her at any time. You are not giving up any of your or your child's legal rights by signing this form. Your signature below indicates that you have read, or had read to you, this entire consent form, including the risks and benefits, and have had all of your questions answered. You will be given a copy of this consent form.

Signature of Parent/ Legally Authorized Guardian	Date
Printed Name of Parent Authorized Guardian	Time
**Signature of Witness (When applicable)	Date
Printed Name of Witness	Time
Signature of Person Obtaining Consent	Date
Printed Name of Person Obtaining Consent	Time

** Use when parent has had consent form read to them (i.e., illiterate, legally blind, translated into foreign language).