From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT questions
Date: Thursday, July 01, 2004 9:25:16 AM

I received this email. I asked her is she spoke with O'Shea however, was unsure if the centers received their notice. They would like one more than what was budgeted for them.

-----Original Message-----
From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, June 30, 2004 6:29 PM
To: Petrie, Carolyn
Cc: Wade Rich
Subject: SUPPORT questions

I wondered if any plans had been made about preparing for the SUPPORT Trial. We do not have NeoPuffs (or a similar device) at either of our sites so we would like to request that we be considered on the list to receive four of these devices, if possible. This would allow us to offer identical delivery room resuscitation to moms with multiples and have one at our second site for those infants that get transferred from site one (delivery hospital) to site two (regional referral center---transfers done for medical and "space" reasons). I did not know if there would be a negotiated price for this equipment from the supplier and if not, what is the monetary allowance for making our purchase. If there is a timeline for when we will receive this information then please let me know so I can plan accordingly....and not "bother" you with our questions.

As always, thanks for your help.

Nancy P.

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD)
Subject: shipping oximeters
Date: Tuesday, July 06, 2004 12:47:57 PM

Rose,
I am shipping oximeters to the pilot sites. Should I just use our acct.
or do
you have a Fex-Ex acct.?
Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology
UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-5230

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: SUPPORT training
Date: Tuesday, July 13, 2004 2:08:09 PM

---

no problem

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 07/13/2004 11:02:09 AM >>>
In an effort to have full coverage and buy in from the staff, the Houston site has requested to bring 5 people to the training. I fully support this and have told them to bring 5 folks from their two sites. If other sites want to bring more than 4, we should accomodate this. Carolyn and I can make sure the people get evenly distributed if the numbers grow by a lot. Let me know if you have any thoughts on this. I believe that the more enthusiasm we can generate, the more likely chance for success!!
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD); edward.donovan@cchmc.org
Cc: petrie@rti.org
Subject: Re: SUPPORT training
Date: Tuesday, July 13, 2004 10:39:35 PM

I am all for centers bringing as many as Ed can accomodate. In addition, I will be trying to visit some sites that have expressed previous interest.
Be well
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <edward.donovan@cchmc.org>; <nfiner@ucsd.edu>
Cc: <petrie@rti.org>
Sent: Tuesday, July 13, 2004 8:02 AM
Subject: SUPPORT training

> In an effort to have full coverage and buy in from the staff, the Houston
> site has requested to bring 5 people to the training. I fully support this
> and have told them to bring 5 folks from their two sites. If other sites
> want to bring more than 4, we should accomodate this. Carolyn and I can
> make sure the people get evenly distributed if the numbers grow by a lot.
> Let me know if you have any thoughts on this. I believe that the more
> enthusiasm we can generate, the more likely chance for success!!
> Thanks
> Rose
> ----------
> Sent from my BlackBerry Wireless Handheld
>

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT agenda
Date: Wednesday, July 14, 2004 8:53:29 AM

Do you have a draft agenda. Also, should I query Neil, Ed, Betty, Ken, you, Estelle for a call?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 13, 2004 2:17 PM
To: 'petrie@rti.org'; 'bkh@rti.org'
Subject: Re: SUPPORT agenda

I think this is a good idea. We should prepare a skeliton agenda to discuss on the call. When I get back to my office this pm, I can find one that Ed had sent awhile ago.
Thanks
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Petrie, Carolyn <petrie@rti.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Hastings, Betty J. <bkh@rti.org>
CC: Petrie, Carolyn <petrie@rti.org>
Sent: Tue Jul 13 14:11:24 2004
Subject: SUPPORT agenda

Rose and Betty-

Should we set up a conference call to outline the SUPPORT training agenda (with you two, Ed, Neil, Wade and others)? I know this would be most helpful to the folks planning the conference space in Cincinnati.

Thanks!

Carolyn Petrie

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 420

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From:	Higgins, Rosemary (NIH/NICHD)
To:	"petrie@rti.org"
Subject:	FW: SUPPORT Call
Date:	Wednesday, July 14, 2004 10:27:15 AM
Attachments:	Training Plan.doc

Ed's draft
-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Thursday, June 10, 2004 2:22 PM
To: mcw3@cwru.edu; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Kurt Schibler; Vivek Narendran
Subject: Re: SUPPORT Call

Attached is a one page, draft outline of the Sept. Training Plan

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Neil Finer" <nfiner@ucsd.edu> 06/10/2004 12:54:22 AM >>>
Hi Everyone
Here is the most current version. I have tried to ensure that is clean and current.
I would like to discuss the following tomorrow:
1. The agenda for the Steering Committee
2. The PO Pilots
3. The secondaries
4. The data forms
5.The plans for the Cincinnati in-service in September
6. Some details - randomization, PDA, Shock etc
7. Anything you want to add

Be well
Neil

September 14, 15, 16 Training Plan **DRAFT**

Objectives

1. Review protocol in detail with implementation perspective

    - Recruitment strategies: enrollment in prenatal clinic, antepartum testing unit, antepartum at risk unit, triage, labor & delivery
    - Discuss how to approach and handle reporting of women who go beyond 27 weeks GA
    - Team approach to delivery room initiation of study in DR
    - Extubation to CPAP
    - Insuring compliance with intubation/weaning/extubation procedures

2. Review technical aspects of DR application of CPAP
3. Review transport to the NICU of infants receiving CPAP
4. Review maintenance of CPAP vis a vis other aspects of care: feeding, positioning, management of apnea, placement and care of vascular catheters and IVs etc.
5. Review teaching video which will be taken back to each center for staff teaching
6. Review CPAP problems and their management: maintaining ordered pressure, nasal erosions, overdistension/pneumothorax
7. Other

Organization

- ½ of group on Tues/Weds and ½ on Weds/Thurs
- Tues and Thurs are to discuss and demonstrate practical issues: CPAP (DR, transport, NICU), recruitment and enrollment, study compliance, etc.
- Each group will be divided in half, ie approximately 16 per group, with half at University Hospital and half at Good Samaritan Hospital
- Shuttles will be provided between training sites and hotel
- Weds is to review forms, IRB submissions, consent forms, etc., etc.

Extras

- Social event on Weds organized so that as many as possible of both groups can attend
- Lectures with CME/CEU during the lunch break – also with time for interaction and discussion: Tues. = "Population-based Perinatal Care: The Cincinnati Model" (Jim Greenberg); Weds. = "Genetic Bases of Pulmonary Biology" (Jeff Whitsett); Thurs. = "The State of Academic Pediatrics" (Tom Boat)

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD); Hastings, Betty J.; Petrie, Carolyn
Cc: Poole, W. Kenneth
Subject: RE: Scheduling SUPPORT Training call (agenda)
Date: Wednesday, July 14, 2004 2:52:14 PM

Ed Donovan is unable to attend this call. I am currently finding times that Ed and Neil are available.

Will send another email shortly.

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Wednesday, July 14, 2004 2:05 PM
> **To:** 'Hastings, Betty J.'; Petrie, Carolyn
> **Cc:** Kenneth Poole (Poole, W. Kenneth)
> **Subject:** RE: Scheduling SUPPORT Training call (agenda)
>
> It is a slightly different group, but perhaps we could do it.
> Rose
>
> > -----Original Message-----
> > **From:** Hastings, Betty J. [mailto:bkh@rti.org]
> > **Sent:** Wednesday, July 14, 2004 2:02 PM
> > **To:** Petrie, Carolyn
> > **Cc:** Higgins, Rosemary (NIH/NICHD); Kenneth Poole (Poole, W. Kenneth)
> > **Subject:** RE: Scheduling SUPPORT Training call (agenda)
> >
> > Carolyn,
> > Could this be combined with the SUPPORT call that is already scheduled for Monday the 19th?
> >
> > > -----Original Message-----
> > > **From:** Petrie, Carolyn
> > > **Sent:** Wednesday, July 14, 2004 1:59 PM
> > > **To:** aRose Higgins (higginsr@mail.nih.gov); Poole, W. Kenneth; M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. Neil Finer (nfiner@ucsd.edu); Wade Rich (wrich@ucsd.edu); Hastings, Betty J.; 'Estelle Fischer'
> > > **Cc:** Petrie, Carolyn
> > > **Subject:** Scheduling SUPPORT Training call (agenda)
> > >
> > > We would like to schedule a conference call to discuss the SUPPORT training agenda. Please send me your availability for the following dates:
> > >
> > > Fri Jul 16
> > >
> > > Mon Jul 19
> > > Tue Jul 20
> > > Wed Jul 21
> > > Thur Jul 22
> > > Fri Jul 23
> > >
> > > Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Neil Finer
To: Higgins, Rosemary (NIH); Wally Carlo
Date: Wednesday, July 14, 2004 3:27:18 PM

Hi Rose
There are essentially 2 pilots. The first, Wally's will compare the SpO2 achieved using the altered POs on about 100 infants each studied for 24 hours.
We believe that the oximeters that have been sent to the sites, 4 to each of the 5 centers, should be paid for from the Pilot budget – 20 X 2000 = $40,000. These would be maintained at the sites for the actual SUPPORT Trial, and thus would not be an additional cost for SUPPORT. We have only been able to estimate the number of oximeters required for SUPPORT, and depending on when they are discontinued, (see my email of yesterday) there may be a need for more. We are trying to do better estimates, but I think that we may need as many as 250 oximeters.
The other costs of the pilot, setup and removal of the oximeter will take 1 hour, approximately 3 hours for attendance during the acquisition, and completion of the data form. There will be 100 patients, and 4 hours per patient would result in 400 hours.
For the other pilot conducted here and at Sharp, we plan to study 20 patients using both oximeters on a patient. We believe that 4 hours per patient is appropriate, and we have the oximeters. Thus this pilot should require 80 hours of time.
I have discussed with Wally and he is OK with these estimates.
Regards
Neil

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Cc: wrich@ucsd.edu
Date: Wednesday, July 14, 2004 6:41:31 PM

Hi Rose
The Neopuff will cost the centers $495.00 US, and the circuit prices will be available shortly, and Wade will forward these when available.
We have not yet received an answer regarding the Masimo probes but will also forward this ASAP.
Regards
Neil

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Cost of sensors for SUPPORT
Date: Thursday, July 15, 2004 10:14:23 AM

Do you want me to see what folks are paying now, to see if there is a significant cost diff? If not it is a moot point and we will just have the clinical folks pay.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 15, 2004 7:08 AM
To: 'Wade Rich'
Cc: 'Neil Finer'
Subject: RE: Cost of sensors for SUPPORT

Wade
I will get input from our grants management office.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 9:59 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: 'Neil Finer'
Subject: RE: Cost of sensors for SUPPORT

Rose,
You are absolutely correct that it is the standard of care.
The problem is that many sites are under contract with a specific oximeter manufacturer for probes.
The individual department may never see an invoice or know what is paid.
By contract they may not
use another oximeter in that hospital. So, if the choose to do a study with an alternative oxim.,
they do not get probes supplies and must pay themsleves, quite possible more than they were paying
for the contracted probe. I guess I would say that is a cost that has been created due to the carrying out of the study.
I will, of course, do as you wish.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 15, 2004 6:47 AM
To: 'Wade Rich'
Cc: Neil Finer (E-mail)
Subject: RE: Cost of sensors for SUPPORT

Wade
Each site can order there own. On another matter, an oximeter probe is part of standard care for infants < 1000 grams. This should probably come out of clinical dollars at the sites.

Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 9:36 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: Cost of sensors for SUPPORT

Rose,
Do you want to deal with Maribeth re: answers. or do you want us to. I would assume we will seed each site
with enough to get started, then let them order as they need them.
Wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Wednesday, July 14, 2004 5:38 PM
To: Wade Rich (E-mail)
Cc: Mike Petterson; Joe Kiani; Neil Finer (E-mail)
Subject: Cost of sensors for SUPPORT

Hi Wade,

The cost of the sensors for SUPPORT is our lowest cost: $12.00 each. Do you want each hospital to order sensors, or will you order them all? If you order them all, we could ship them to hospitals as you direct. This would allow you to keep control and know which hospital got sensors, and how many.

Maribeth

Maribeth P. Sayre, M.D.
Director of Medical Affairs
Masimo Corporation
Cell (925)337-3856
Email: msayre@Masimo.com

****

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD)
Cc:	wrich@ucsd.edu
Subject:	RE: Cost of sensors for SUPPORT
Date:	Thursday, July 15, 2004 12:56:02 PM

Rose this should be less of an issue in view of the pricing from Masimo which makes their probes cheaper than the competition at least for the trial sites.
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 15, 2004 7:53 AM
To: 'Wade Rich'
Cc: Neil Finer (E-mail); Hickman, Leslie (NIH/NICHD)
Subject: RE: Cost of sensors for SUPPORT

Wade
Each site should purchase their own probes - they can use a portion of the capitation funds for this or, depending on the site, have the clinical enterprise purchase them.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 10:14 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Cost of sensors for SUPPORT

Do you want me to see what folks are paying now, to see if there is a significant cost diff? If not it is a moot point and we will just have the clinical folks pay.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 15, 2004 7:08 AM
To: 'Wade Rich'
Cc: 'Neil Finer'
Subject: RE: Cost of sensors for SUPPORT

Wade
I will get input from our grants management office.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 9:59 AM
To: Higgins, Rosemary (NIH/NICHD)
Cc: 'Neil Finer'
Subject: RE: Cost of sensors for SUPPORT

Rose,
You are absolutely correct that it is the standard of care.
The problem is that many sites are under contract with a specific oximeter manufacturer for probes.
The individual department may never see an invoice or know what is paid.
By contract they may not
use another oximeter in that hospital. So, if the choose to do a study with an alternative oxim.,
they do not get probes supplies and must pay themsleves, quite possible more than they were paying
for the contracted probe. I guess I would say that is a cost that has been created due to the carrying out of the study.
I will, of course, do as you wish.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 15, 2004 6:47 AM
To: 'Wade Rich'
Cc: Neil Finer (E-mail)
Subject: RE: Cost of sensors for SUPPORT

Wade
Each site can order there own. On another matter, an oximeter probe is part of standard care for infants < 1000 grams. This should probably come out of clinical dollars at the sites.
Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 9:36 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: Cost of sensors for SUPPORT

Rose,
Do you want to deal with Maribeth re: answers. or do you want us to. I would assume we will seed each site
with enough to get started, then let them order as they need them.
Wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Wednesday, July 14, 2004 5:38 PM
To: Wade Rich (E-mail)
Cc: Mike Petterson; Joe Kiani; Neil Finer (E-mail)
Subject: Cost of sensors for SUPPORT

Hi Wade,

The cost of the sensors for SUPPORT is our lowest cost: $12.00 each. Do you want each hospital to order sensors, or will you order them all? If you order them all, we could ship them to hospitals as you direct. This would allow you to keep control and know which hospital got sensors, and how many.

Maribeth

Maribeth P. Sayre, M.D.
Director of Medical Affairs
Masimo Corporation
Cell (925)337-3856
Email: msayre@Masimo.com

****

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Training
Date: Friday, July 16, 2004 11:53:53 AM

If the group chooses a disk/tape format, do you think we could set up the internet access with the RTI website (in addition)?

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, July 16, 2004 11:37 AM
To: Self; kathy.auten@duke.edu; grisbyca@email.uc.edu; dappel@iupui.edu; jlemons@iupui.edu; lucmille@iupui.edu; mbball@leland.stanford.edu; higginsr@mail.nih.gov; goldb008@mc.duke.edu; lsmith3@med.miami.edu; r.everett@med.miami.edu; sshankar@med.wayne.edu; sduara@miami.edu; ellen_hale@oz.ped.emory.edu; gmcdavid@ped1.med.uth.tmc.edu; mcollins@peds.uab.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; nxs5@po.cwru.edu; poo@rti.org; dstevenson@stanford.edu; chenderson@ucsd.edu; nfiner@ucsd.edu; dale_phelps@urmc.rochester.edu; linda_reubens@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; gaynelle.hensley@utsouthwestern.edu; Susie.Madison@utsouthwestern.edu; ae5357@wayne.edu; moshea@wfubmc.edu; npeters@wfubmc.edu; ahensman@wihri.org; ALaptook@wihri.org; WOh@wihri.org; pat.gettner@yale.edu; Richard.Ehrenkranz@yale.edu
Cc: Estelle Fischer; petrie@rti.org
Subject: SUPPORT Training

We are developing some cost estimates for producing a SUPPORT training video that you could be used for educating clinicians in your center.

Imagine a night shift nurse or therapist with a SUPPORT baby in the CPAP arm of the study. He or she wants some info on the study and managing the nasal CPAP device during routine care.

If a training video were available, what format would be most appropriate in your NICU? Choices would be high speed Internet connection, DVD, CD or VHS.

Let me know.
Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Cost of Masimo sensors for SUPPORT
Date: Monday, July 19, 2004 8:58:01 AM

I actually ask the coordinators in case someone else does the ordering.
Thanks.
Wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 19, 2004 5:56 AM
To: 'Wade Rich'; 'bkh@rti.org'
Subject: RE: Cost of Masimo sensors for SUPPORT

Wade,
I will have Betty Hastings forward a list of the sties to you. Thanks
Rose

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Monday, July 19, 2004 8:51 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Cost of Masimo sensors for SUPPORT

FYI.

Wade,

I have talked to Vickie Bishop, our Customer Service supervisor. Could you send us a list of all the hospitals with the full name of the hospital (sorry I can't figure out some of the initials), the city wherein the hospital is located, and the contact person for the hospital, ie the person who will be doing the ordering. Vickie will then put all this in her system and idintify them as NICHD SUPPORT clients with the $12 sensor pricing. Vickie will then be able to tract the sensor orders for each hospital. She will probably have a special order number. She is working on this. Will keep you informed as the system developes.

Maribeth

-----Original Message-----
From: Wade Rich [mailto:wrich@ucsd.edu]
Sent: Thursday, July 15, 2004 7:01 AM
To: 'Maribeth Sayre'
Subject: RE: Cost of sensors for SUPPORT

Each site is responsible for their own budget, so they will order their own. How should
they order them so as to get this price. Will you have a number which identifies the
sensors as going to the NICHD trial?
Wade

-----Original Message-----
From: Maribeth Sayre [mailto:MSayre@masimo.com]
Sent: Wednesday, July 14, 2004 5:38 PM
To: Wade Rich (E-mail)
Cc: Mike Petterson; Joe Kiani; Neil Finer (E-mail)
Subject: Cost of sensors for SUPPORT

Hi Wade,

The cost of the sensors for SUPPORT is our lowest cost: $12.00 each. Do you want each hospital to order sensors, or will you order them all? If you order them all, we could ship them to hospitals as you direct. This would allow you to keep control and know which hospital got sensors, and how many.

Maribeth

Maribeth P. Sayre, M.D.
Director of Medical Affairs
Masimo Corporation
Cell (925)337-3856
Email: msayre@Masimo.com

****

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD)
Cc: Poole, W. Kenneth
Subject: RE: SUPPORT
Date: Tuesday, September 06, 2005 3:09:10 PM

According to the protocol, the first look is at 25%.
Thanks

Abhik

> -----Original Message-----
> **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> **Sent:** Tuesday, September 06, 2005 3:02 PM
> **To:** Das, Abhik
> **Cc:** Poole, W. Kenneth
> **Subject:** RE: SUPPORT
>
> One more question – when is the "first look at the data?" 25% or 33% or something else?
> Thanks
> Rose

> **From:** Das, Abhik [mailto:adas@rti.org]
> **Sent:** Tuesday, September 06, 2005 2:59 PM
> **To:** Higgins, Rosemary (NIH/NICHD)
> **Cc:** Poole, W. Kenneth
> **Subject:** RE: SUPPORT
>
> I think you are correct on the 1st one. As for the 2nd, the DSMC has been discussing the issue by email, but there has not been a resolution. It looks likely that we would have to set up a call to get them to formally make a decision.
>
> Thanks
>
> Abhik
>
> > -----Original Message-----
> > **From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> > **Sent:** Tuesday, September 06, 2005 2:50 PM
> > **To:** Das, Abhik; Poole, W. Kenneth
> > **Subject:** SUPPORT
> >
> > Ken and Abhik,
> > For the SUPPORT babies, Neil was asking if the PI's were going to see the safety data – I told him I thought not, but that the DSMC would look at it if needed.- Correct??
> >
> > For Wally's secondary, did the DSMC weigh in on whether or not we could see these data, even in a blinded fashion??
> > Thanks
> > Rose
> >
> > Rosemary D. Higgins, M.D.
> > Program Scientist for the Neonatal Research Network
> > Pregnancy and Perinatology Branch
> > Center for Developmental Biology and Perinatal Medicine
> > NICHD, NIH

6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(For overnight delivery, use Rockville, MD 20852)
301-435-7909
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT visits by Dr.Sayre
Date: Thursday, November 03, 2005 9:20:28 AM

You are very welcome!

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 03, 2005 9:17 AM
To: Das, Abhik
Subject: Re: SUPPORT visits by Dr.Sayre

Thanks Abhik,
Sorry for all the trouble.
I really appreciated your quick responses, candor and help!! Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>;
wrich@ucsd.edu <wrich@ucsd.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>
Sent: Thu Nov 03 09:16:00 2005
Subject: RE: SUPPORT visits by Dr.Sayre

I think Wade's memo, with the corrections suggested by Rose, is fine.

Thanks

Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 03, 2005 9:13 AM
To: wrich@ucsd.edu; nfiner@ucsd.edu; Das, Abhik
Subject: Re: SUPPORT visits by Dr.Sayre

Change the last sentence to
"Data and patient information with respect to the SUPPORT trial are to
be treated as CONFIDENTIAL and should not be communicated with Masimo
company personnel."

Also, wait to hear from Abhik also on this one.

Thanks for your attention to this!!
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>

To: nfiner@ucsd.edu <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Thu Nov 03 09:08:36 2005
Subject: FW: SUPPORT visits by Dr.Sayre

Rose, Neil,

I was going to send this to sites and Maribeth. Can you review? Thanks.

Coordinators at more than one site have asked me why we have scheduled visits from Maribeth Sayre at Masimo for Support centers. Please be advised that
these visits are being planned, carried out, and paid for by Masimo. The are not related to the study in any way. If you need help with your oximeters, you may
call Maribeth as you always have and she will assist you as best she can. You may treat any visits initiated by Masimo as a sales call, and treat them as you would any other visit from a company representative. You should not, at the request of Dr. Higgins, discuss patient information or study data with Dr. Sayre.

Thank you,
Wade Rich

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 02, 2005 9:42 PM
To: 'Higgins, Rosemary (NIH/NICHD)'
Cc: 'wade'
Subject: RE: SUPPORT visits by Dr.Sayre

Hi Rose

I have no knowledge of this and there should not be any Masimo visits for SUPPORT. The equipment is bought and paid for, this is not an FDA trial, and they have no role at the sites. In addition I do not want them interfering with the study oximeters. I will ask Wade to call Maribeth and Masimo and clarify.

I am out of town for the next 8 days, but I will try to stay tuned to my email. I'm not sure if I will be able to do this. If necessary I will call her myself.

Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 02, 2005 12:03 PM
To: Nancy Peters
Cc: nfiner@ucsd.edu; moshea@wfubmc.edu; Das, Abhik
Subject: RE: SUPPORT visits by Dr.Sayre

Hi Nancy,

It is my understanding that Dr. Sayre is with Massimo, correct? If so, she should discuss only the equipment. No patient information or study data can be shared with her.

Thanks for asking!
Rose

From: Nancy Peters [mailto:npeters@wfubmc.edu]
Sent: Wednesday, November 02, 2005 2:09 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT visits by Dr.Sayre

Rose,

Just curious as to the nature of the SUPPORT Study visits that Dr. Maribeth Sayre is scheduling. Is this just a PR meet and greet and tour of the sites at our center? She did mention that she wanted to know if we had any problems or suggestions --- and I assume that only deals with the Masimo equipment, not other study issues. What information is she privy to? A few guidelines would be helpful.

Thank you.

Nancy P.

From:	Petrie, Carolyn
To:	"M. D. Abbot Laptook (alaptook@WIHRI.org)"; "M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu)"; "M. D. Michael O"Shea (moshea@wfubmc.edu)"; "M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu)"; "M. D. Ronald Goldberg (goldb008@mc.duke.edu)"; "William Oh2 (WOh@wihri.org)"
Cc:	"Angelita Hensman (ahensman@wihri.org)"; "Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu)"; "Pat Gettner (pat.gettner@yale.edu)"; "RN Kathy Auten (auten002@mc.duke.edu)"; "RN Nancy Peters (npeters@wfubmc.edu)"; Higgins, Rosemary (NIH/NICHD); Petrie, Carolyn
Subject:	RE: SUPPORT Training
Date:	Tuesday, June 01, 2004 9:59:26 AM

Dear All from Brown, Duke, Yale, Wake Forest, and Houston:

We are in the early stages of planning the SUPPORT training, to be held in Cincinnati.

We hope that the key staff will be able to attend this training (e.g. Study PI, Coordinator, Respiratory Therapist and/or Head Nurse). Please indicate your and your staff's availability for the following series of dates:

Sept 7 & 8
Sept 8 & 9

Sept 14 & 15
Sept 15 & 16

Ideally, we would like half of the centers to attend the first two days and the other half the last two days (middle day overlapping with all centers).

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: support
Date: Tuesday, June 01, 2004 11:17:46 AM
Attachments: SUPPORT Training Votes.xls

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

	Sept 7 & 8	Sept 8 & 9	Sept 14 & 15	Sept 15 & 16
Case			x	x
Texas-Hstn				
Texas-Dls	x	x		
Wayne St	x	x	x	x
Miami			x	x
Emory			x	
				x
Cincinnati*	x	x	x	x
Indiana	x			
Yale				
Brown				
Stanford			x	x
Alabama	x	x	x	
Duke				
WFU				
Rochester	x	x	x	x
UCSD*	x	x	x	x
hastings			x	x

*did not respond but assume they are available all dates

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: reconciled support budget
Date: Tuesday, June 01, 2004 5:32:58 PM
Attachments: Support DRCPAP reconcile 2004 A budget.xls

See attached.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

FY2041- A Support DR CPAP DRAFT BUDGET

	Start-up + training	TRIAL Estimated number of total pts	Equipment	Supplies	*Ventilation* Data collection @$1000/pt	Total direct	Indir Factor	Indirect $$	**2004 A Award RECONCILE Study Costs (Not Training)**
Case*	$2,000	33			$33,000	$33,000	0.53	$17,490	-$48,490
Texas-Hstn	$2,000	40	$5,000	$500	$40,000	$45,500	0.495	$22,523	-$66,023
Texas-Dls	$2,000	28	$5,000	$500	$28,000	$33,500	0.56	$18,760	-$50,260
Wayne St	$2,000	33	$5,000	$500	$33,000	$38,500	0.49	$18,865	-$55,365
Miami*	$2,000	45			$45,000	$45,000	0.515	$23,175	-$66,175
Emory	$2,000	28	$5,000	$500	$28,000	$33,500	0.28	$9,380	-$40,880
Cincinnati*	$2,000	40			$40,000	$40,000	0.53	$21,200	-$59,200
Indiana	$2,000	40	$5,000	$500	$40,000	$45,500	0.49	$22,295	-$65,795
Yale	$2,000	13	$5,000	$500	$13,000	$18,500	0.299	$5,532	-$22,032
Brown	$2,000	33	$5,000	$500	$33,000	$38,500	0.393	$15,131	-$51,631
Stanford	$2,000	18	$5,000	$500	$18,000	$23,500	0.6	$14,100	-$35,600
Alabama*	$2,000	50			$50,000	$50,000	0.435	$21,750	-$69,750
WFU	$2,000	48	$5,000	$500	$48,000	$53,500	0.45	$24,075	-$75,575
Duke	$2,000	33	$5,000	$500	$33,000	$38,500	0.54	$20,790	-$57,290
Rochester	$2,000	28	$5,000	$500	$28,000	$33,500	0.595	$19,933	-$51,433
UCSD*	$2,000	50			$50,000	$50,000	0.515	$25,750	-$73,750
Totals	**$32,000**	560	**$55,000**	**$5,500**		**$620,500**		**$300,747**	**-$889,247**

*Pilot enters; funds for all other centers restricted

From:	Edward Donovan
To:	bkh@rti.org; petrie@rti.org
Cc:	Diane Timmer; Estelle Fischer; James Greenberg; Janel Chriss; Higgins, Rosemary (NIH/NICHD)
Subject:	SUPPORT Trial
Date:	Tuesday, June 01, 2004 6:11:53 PM

Carolyn and Betty,

We are a little uncertain about who will be doing what in preparation for the SUPPORT training.

Here's what's going on from our end:

Two groups coming - one Tues. and Wed. Sept. 14/15 and one Weds and Thurs. Sept. 15/16.

We are holding rooms at the Marriott Kingsgate on our campus for Monday, Tues., Weds and Thurs. Janel Chriss is the contact (copied on this email). She wonders whether we need breakout rooms on Weds.?

We are planning three talks with CME/CEU during the three lunches (box lunches?).
Jim Greenberg, Dir. Div of Neonatology - "Population based neonatal care in Cincinnati"
Jeff Whitsett, "The genomics of pulmonary biology"
Tom Boat, topic?

We are working on a 20-30 minute training video that folks can take back for staff education/PR.

We will break each of Tues and Thurs into 4 pieces - 2 at Univ. Hosp. and 2 at Good Sam. 1/4th of the group will view and hear about CPAP applications in the DR and NICU at UH; 1/4th will do a practicum using models at UH; the other 2 1/4ths will do the same at Good Sam.

We're going to arrange for shuttles between sites (less than 1 mile apart).

We're planning a social "get together" before dinner on Weds. night downtown in the restaurant district so that afterwords folks can go to a rest. of their choice.

Diane will be working on a draft, overview agenda/timetable. We are assuming that we can start 9:30 or 10 on Tues. and start earlier and end earlier on Thurs. so that folks can get to the airport.

Estelle is helping keep track of budget issues.

We are incredibly excited that the Network has selected Cincinnati for the training site.

We want to do whatever we can to see that this goes well.
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From:	Hastings, Betty J.
To:	Higgins, Rosemary (NIH/NICHD)
Cc:	Petrie, Carolyn
Subject:	Dr. Donovan"s message-Training
Date:	Wednesday, June 02, 2004 10:58:29 AM
Attachments:	Training agenda July 00.doc

Rose/Carolyn,
I was getting ready to respond to Dr. Donovan's message however, I'm uncertain as to why we're meeting in two groups for 3 days. Is it just because the group will be so large? It would seem to me that we would, at some point, want the entire group together for reviewing the data forms, manual, etc.

When we had training for Preemie we met for one day (I believe) and the group was divided into 2 parts. Group I attended the first session in the morning and second in the afternoon, Group II did the reverse.

I'm attaching a draft agenda from that training.
Thanks.
Betty

<<Training agenda July 00.doc>>

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

NICHD Training Meeting
Inhaled Nitric Oxide for Preterm Infants with Severe Respiratory Failure

Munzer Auditorium
Beckman Building
July 10, 2000

8:30 –9:00	Introduction	Linda Wright, M.D.
9:00 – 11:00	Protocol review	Krisa Van Meurs, M.D.
11:00 – 11:30	Questions and quiz	Krisa Van Meurs, M.D. Bethany Ball
11:30 –12:00	Suggestions for study screeing and RT training	Bethany Ball Bill Callas, RRT
12:00 – 1:00	Lunch	

The group is divided into 2 parts and Group I attends first session I from 1:00 – 2:00 PM and then Session II from 2:00 – 3:00 PM. Group II does the reverse.

Session I is located in NICU Conference Room on the second floor of Packard Children's Hospital and Session II is located in the PICU Conference Room also on the second floor of the Children's Hospital. Maps will be provided at lunch.

Session I	Review of Manual, forms and randomization procedures	Ken Poole
Session II	Blinding procedures, equipment review and study gas management	Rebecca Enos Jeff Schmidt, R.R.T.

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: drcpap
Date: Wednesday, June 02, 2004 11:20:06 AM
Attachments: DRCPAP pilot closeout 2004 A budget.xls

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

FY2003 A DR CPAP DRAFT BUDGET per patient reconciliation

	Estimated # Pilot patients	Data collection (4hrs@$32/hr)	subtotal direct pilot	Indir Factor	Indirect Costs	Total Pt award	Actual # of Pts enrolled	Diff	Data collection (4hrs@$32/hr)	subtotal direct pilot	Indir Factor	Indirect Costs	Total Pt award	Reconciled FY 2003 Pil
Case*	20	$2,560	$2,560	0.53	$1,357	$3,917	11	(9)	$1,408	$1,408	0.53	$746	$2,154	($1,763)
Texas-Hstn														
Texas-Dls														
Wayne St														
Miami*	30	$3,840	$3,840	0.515	$1,978	$5,818	29	(1)	$3,712	$3,712	0.515	$1,912	$5,624	($194)
Emory														
Cincinnati*	25	$3,200	$3,200	0.53	$1,696	$4,896	12	(13)	$1,536	$1,536	0.53	$814	$2,350	($2,546)
Indiana														
Yale														
Brown														
Stanford														
Alabama*	35	$4,480	$4,480	0.435	$1,949	$6,429	32	(3)	$4,096	$4,096	0.435	$1,782	$5,878	($551)
WFU														
Duke														
Rochester														
								0						
UCSD*	40	$5,120	$5,120	0.515	$2,637	$7,757	20		$2,560	$2,560	0.515	$1,318	$3,878	($3,878)
Totals	150	**$19,200**	**$19,200**	**0.51**			**104**		**$13,312**	**$13,312**				**($8,932)**

FY2001- B DR CPAP DRAFT BUDGET

	Estimated # Pilot patients	PILOT Start-up	Equipment	Supplies	Data collection (4hrs@$32/hr)	subtotal direct pilot	Start-up + training	TRIAL Estimated umber of total pts	Equipment	Supplies	*Ventilation* Data collection @$1000/pt	Total direct	Indir Factor	Indirect $$	2001-B TOTAL
Case*	20	2000	$5,000	$500	$2,560	$10,060	$2,000	33			$33,000	$43,060	0.53	$22,822	$65,882
Texas-Hstn							$2,000	40	$5,000	$500	$40,000	$45,500	0.495	$22,523	$68,023
Texas-Dls							$2,000	28	$5,000	$500	$28,000	$33,500	0.56	$18,760	$52,260
Wayne St							$2,000	33	$5,000	$500	$33,000	$38,500	0.49	$18,865	$57,365
Miami*	30	2000	$5,000	$500	$3,840	$11,340	$2,000	45			$45,000	$56,340	0.515	$29,015	$85,355
Emory							$2,000	28	$5,000	$500	$28,000	$33,500	0.28	$9,380	$42,880
Cincinnati*	25	2000	$5,000	$500	$3,200	$10,700	$2,000	40			$40,000	$50,700	0.53	$26,871	$77,571
Indiana							$2,000	40	$5,000	$500	$40,000	$45,500	0.49	$22,295	$67,795
Yale							$2,000	13	$5,000	$500	$13,000	$18,500	0.299	$5,532	$24,032
Brown							$2,000	33	$5,000	$500	$33,000	$38,500	0.393	$15,131	$53,631
Stanford							$2,000	18	$5,000	$500	$18,000	$23,500	0.6	$14,100	$37,600
Alabama*	35	2000	$5,000	$500	$4,480	$11,980	$2,000	50			$50,000	$61,980	0.435	$26,961	$88,941
WFU							$2,000	48	$5,000	$500	$48,000	$53,500	0.45	$24,075	$77,575
Duke							$2,000	33	$5,000	$500	$33,000	$38,500	0.54	$20,790	$59,290
Rochester							$2,000	28	$5,000	$500	$28,000	$33,500	0.595	$19,933	$53,433
UCSD*	40	2000		$500	$5,120	$7,620	$2,000	50			$50,000	$57,620	0.515	$29,674	$87,294
Totals	150		**$20,000**	**$2,500**	**$19,200**	**$51,700**	**$32,000**	560	**$55,000**	**$5,500**		**$672,200**		**$326,726**	**$998,926**

*Pilot enters; funds for all other centers restricted

From:	Hastings, Betty J.
To:	"Angelita Hensman (ahensman@wihri.org)"; "Bethany Ball (mbball@leland.stanford.edu)"; "Cathy Grisby (grisbyca@email.uc.edu)"; "Ellen Hale (ellen_hale@oz.ped.emory.edu)"; "Gay Hensley (gaynelle.hensley@utsouthwestern.edu)"; "Georgia E McDavid"; "Gerry Muran (ae5357@wayne.edu)"; "Kathy Auten (auten002@mc.duke.edu)"; "Linda Reubens (linda_reubens@urmc.rochester.edu)"; "Lucy Miller (lucmille@iupui.edu)"; "Monica Collins (mcollins@peds.uab.edu)"; "Nancy Miller (Nancy.Miller@UTSouthwestern.edu)"; "Nancy Newman"; "Nancy Peters (npeters@wfubmc.edu)"; "Pat Gettner (pat.gettner@yale.edu)"; "Rebecca Bara (ae5357@wayne.edu)"; "RNC Kathy Arnell (kathy.arnell@sharp.com)"; "Ruth Everett (Reverett@med.miami.edu)"; Barbara Alexander (balexanba@hotmail.com); "Lenora Jackson"; "Estelle E. Fischer"; "Holly Mincey"; "Jody Shively"; "Kate Bridges, MD"
Cc:	"Wade Rich (wrich@ucsd.edu)"; Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD)
Subject:	Query from Wade Rich and Dr. Finer
Date:	Thursday, June 03, 2004 12:33:06 PM

From Wade Rich:

Please send your responses to Wade wrich@ucsd.edu

Dear Friends (aka Study Coordinators),

In order to provide the most appropriate in-service for the SUPPORT training in Cincinnati this summer, we need to know the answer to the following questions.

1) Do you currently provide CPAP in the Delivery Room?
2) If so, what device/instrument do you use to provide it.
3) Do you use the same device to transport the infant to the NICU?

Thanks for your help.
Wade

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

Blansfield, Earl (NIH/NICHD) [E]

From: Edward Donovan <Edward.Donovan@cchmc.org>
Sent: Thursday, June 03, 2004 10:40 AM
To: Diane Timmer
Subject: SUPPORT Training

Diane,
Please forward this to everyone on the SUPPORT Training planning committee, as well as to Rose Higgins, Carolyn Petrie, the 3 speakers, Barb Warner, Kurt Schibler, the Network Research Coordinators and Leslie Altemier.
Thanks,
Ed

FYI.
We have lined up our lunch speakers for the SUPPORT Training!
On Tues. Sept. 14, Jim Greenberg
On Weds. Sept. 15, Jeff Whitsett
On Thurs. Sept. 16, Tom Boat

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From:	Diane Timmer
To:	Barbara Warner; Cathy Grisby; Estelle Fischer; James Greenberg; Janel Chriss; Jean Steichen; jeff.whitsett@cchmc.org; Kurt Schibler; Thomas Boat; Vivek Narendran; daviske@healthall.com; FisherPD@healthall.com; HegnerCJ@healthall.com; mcclans@healthall.com; Higgins, Rosemary (NIH/NICHD); petrie@rti.org; pam@savethegonads.com; Leslie_Altimier@Trihealth.com; barbara.alexander@uc.edu; mincevhl@uc.edu
Subject:	Fwd: SUPPORT Training
Date:	Thursday, June 03, 2004 1:28:32 PM
Attachments:	SUPPORT Training.msg

FYI.
We have lined up our lunch speakers for the SUPPORT Training!
On Tues. Sept. 14, Jim Greenberg
On Weds. Sept. 15, Jeff Whitsett
On Thurs. Sept. 16, Tom Boat

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171

Diane Timmer
Executive Secretary
Child Policy Research Center
Cincinnati Children's Hospital Medical Center
ML-7014
3333 Burnet Ave.
Cincinnati, OH 45229
513-636-0169
513-636-0171 Fax
email: diane.timmer@cchmc.org

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; Charles Rosenfeld (crosen@mednet.swmed.edu); M. D. Abbot Laptook (alaptook@WIHRI.org); M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Avroy A. Fanaroff (aaf2@cwru.edu); [SCRN] Stoll, Barbara; M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Cathy Grisby (Cinn) (grisbyca@email.uc.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); Gerry Muran (ae5357@wayne.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); (Nancy.Miller@UTSouthwestern.edu); Nancy Newman (nxs5@cwru.edu); Pat Gettner (pat.gettner@yale.edu); RN Kathy Auten (auten002@mc.duke.edu); RN Linda Reubens (linda_reubens@urmc.rochester.edu); RN Nancy Peters (npeters@wfubmc.edu); Ruth Everett (reverett@med.miami.edu); Wade Rich (wrich@ucsd.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. Michael O"Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ronald Goldberg (goldb008@mc.duke.edu); M. D. Shahnaz Duara (sduara@miami.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Walid A. Salhab (Walid.Salhab@UTsouthwestern.edu); Michele Walsh (mcw3@cwru.edu); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org); Brenda Morris MD (Brenda.H.Morris@uth.tmc.edu); M. D. Krisa VanMeurs (vanmeurs@leland.stanford.edu); Susie Buchter (susie.buchter@oz.ped.emory.edu); Vivek Narendran (Vivek.Narendran@cchmc.org); Mike Cotten (cotte010@mc.duke.edu); "nirupama_laroia@urmc.rochester.edu"; (vineet.bhandari@yale.edu); Hastings, Betty J.; Das, Abhik; "Estelle.Fischer@cchmc.org"
Cc:	Petrie, Carolyn; Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)
Subject:	SUPPORT Training Participants List
Date:	Thursday, June 03, 2004 1:53:29 PM
Attachments:	SUPPORT Training Participants List v6_3_04.doc

Please find the Participants List for the SUPPORT Training, to be hosted in:
Cincinnati, OH
September 14-16, 2004.

If your group would like to switch dates or if any changes should be made to your center's participants list, please let me know by **Friday, June 18th**.

This email has been sent to the following groups of people:

1) Neonatal Research Network PIs
2) Designated site PIs
3) Neonatal Research Network Coordinators

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

SUPPORT Training
Cincinnati, OH

September 14 and 15, 2004

Texas-Houston
Dr. Brenda Morris, Georgia McDavid

Texas-Dallas
Dr. Walid Salhab, James Allen, Gaynelle Hensley, Della Feeha

Miami
Dr. Shahnaz Duara, Ruth Everett, Lucille Fasone, Janet Mitchell

Cincinnati
Dr. Vivek Narendran, Cathy Grisby

Yale
Dr. Vineet Bhandari, Pat Gettner, Tim Mack, Monica Konstantino

Stanford
Dr. Krisa Van Meurs, Bethany Ball, Dan Proud

Alabama
Dr. Wally Carlo, Monica Collins, Robert Johnson

San Diego
Dr. Neil Finer, Wade Rich, Renee Bridge, Jim Goodmar

RTI
Dr. Ken Poole, Betty Hastings, Carolyn Petrie

NICHD
Dr. Rosemary Higgins

SUPPORT Training

Cincinnati, OH

September 15 and 16, 2004

Case Western
Dr. Michele Walsh, Nancy Newman, Mike Tracey, Bonnie Siner

Wayne St
Dr. Seetha Shankaran, Rebecca Bara, George Benvenuto, Rontriece Turner

Emory
Dr. Susie Buchter, Ellen Hale

Indiana
Dr. James Lemons, Lucy Miller

Brown
Dr. Abbot Laptook, Angelita Hensman, Daniel Gingras, Kim Francis

Wake Forest
Dr. T. Michael O'Shea, Nancy Peters

Rochester
Dr. Nirupama Laroia, Linda Reubens

Duke
Dr. C. Michael Cotten Denise Lawson, Kathy Auten, Kathy Foy

RTI
Dr. Ken Poole, Betty Hastings, Carolyn Petrie

NICHD
Dr. Rosemary Higgins

From:	Edward Donovan
To:	bkh@rti.org
Cc:	Kurt Schibler; Higgins, Rosemary (NIH/NICHD)
Subject:	SUPPORT Training
Date:	Friday, June 04, 2004 6:05:00 PM
Attachments:	Survey of Network center CPAP use in preparation for SUPPORT training v2.doc

Betty,
Attached is the questionnaire for planning the SUPPORT training. It might be best to tabulate these before the upcoming SC meetings so that we could complete any clarifications at that time.
Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

Center _____

Survey of Network centers' CPAP use

The purpose of this questionnaire is to determine the amount and type of experience that your clinical staff has with using non-ET CPAP and to determine the types of CPAP used by Network centers. The answers will help us plan the upcoming SUPPORT training in terms of areas of emphasis, etc. There is no need to do chart reviews for this survey; just give your best approximation. Return to Betty Hastings.

1. For VLBW infants in your center receiving CPAP, what proportion receive ET vs nasal CPAP? [in this case "nasal" refers to nasal prongs, nasopharygeal tube or nasal mask]

   ET CPAP ___%
   Nasal CPAP ___%

2. Do some VLBW infants in your center receive nasal CPAP?

   Yes ___ No ___

   More than 5 infants per month? __
   More than 10 infants per month? __

3. Do some ELBW infants in your center receive nasal CPAP?

   Yes ___ No ___

   More than 5 infants per month? __
   More than 10 infants per month? __

3. What nasal apparatus is most often used for VLBW nasal CPAP in your center?

Short nasal prongs	___	Brand _____
Long nasal prongs	___	Brand _____
Nasopharygeal tube	___	Brand _____
Nasal mask	___	Brand _____
Other	___	Brand _____

4. For VLBW infants receiving CPAP, does CPAP typically begin in the delivery room?

   Yes ___ No ___

5. Roughly how many VLBW infants per month have nasal or mask begun in the delivery room and continued in the NICU? _____

6. Please rank, from most to least common, the indications for CPAP in your nursery:

Management of RDS	___
Management of apnea	___
Management of the post-extubation period	___
Other, explain _____	___

7. What device is most commonly used for delivering CPAP pressure in your center (choose one)?

"Home made" underwater seal	___	Humidified? ___
Other underwater seal	___	Humidified? ___
Commercial CPAP device	___	Humidified? ___
List brand and model_____		
Ventilator	___	Humidified? ___
List brand and model_____		

8. Is CPAP commonly used for more than 3 days in an individual VLBW infant?

   Yes ___ No ___ _____

9. Are VLBW infants in your center fed while receiving CPAP?

   Yes ___ No ___ _____

10. Does your center routinely use an indwelling nasogastric tube in infants receiving nasal CPAP?

    Yes ___ No ___ _____

11. Please provide <u>any comments</u> that you think might be helpful in planning the SUPPORT training – for example, related to such things as factors important to the success of CPAP, problems that you encounter frequently (nasal erosions, prongs falling out, bleeding, adequate seal, plugging), keeping the mouth closed, actually delivering the preset pressure, etc. etc.

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Thanks very much for your help. Return questionnaires to Betty Hastings.

From:	Hastings, Betty J.
To:	M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Abbot Laptook (alaptook@wihri.org); M. D. Avroy A. Fanaroff (aaf2@po.cwru.edu); M. D. Barbara J. Stoll (barbara_stoll@oz.ped.emory.edu); M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. MPH Michael O"Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ron Goldberg (goldb008@mc.duke.edu); M. D. Seetha Shankaran (sshankar@med.wayne.edu); M. D. Shahnaz Duara (sduara@miami.edu); Walid Salhab, MD; Charles Rosenfield, MD; M.D. William Oh; Michele Walsh, MD; Ruth Everett (Reverett@med.miami.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia E McDavid; Gerry Muran (ae5357@wayne.edu); Kathy Auten (auten002@mc.duke.edu); Linda Reubens (linda_reubens@urmc.rochester.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); Nancy Miller (Nancy.Miller@UTSouthwestern.edu); Nancy Newman; Nancy Peters (npeters@wfubmc.edu); Pat Gettner (pat.gettner@yale.edu); RNC Kathy Arnell (kathy.arnell@sharp.com); Wade Rich; Cathy Grisby(grisbyca@email.uc.edu); Barbara Alexander (balexanba@hotmail.com); Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject:	Survey of Network Centers" CPAP use
Date:	Monday, June 07, 2004 10:30:14 AM
Attachments:	Survey of Network center CPAP use.doc

From Dr. Donovan:

In preparation for planning the SUPPORT training session, please complete the attached questionnaire and e-mail or Fax (919-485-7762) to Betty Hastings by Friday, June 11th.

The plan is to tabulate the results prior to the upcoming SC meeting in order for clarifications to be made at that time.

Thanks for your help. <<Survey of Network center CPAP use.doc>>
Betty

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

June 7, 2004

Center:

Date: / /

Contact:

Survey of Network centers' CPAP use

The purpose of this questionnaire is to determine the amount and type of experience that your clinical staff has with using non-ET CPAP and to determine the types of CPAP used by Network centers. The answers will help us plan the upcoming SUPPORT training in terms of areas of emphasis, etc. There is no need to do chart reviews for this survey; just give your best approximation.

Please return this survey to Betty Hastings bkh@rti.org or Fax: (919-485-7762)

1. For VLBW infants in your center receiving CPAP, what proportion receive ET vs nasal CPAP? [in this case "nasal" refers to nasal prongs, nasopharygeal tube or nasal mask]

   ET CPAP %
   Nasal CPAP %

2. Do some VLBW infants in your center receive nasal CPAP?

   Yes No

   More than 5 infants per month?
   More than 10 infants per month?

3. Do some ELBW infants in your center receive nasal CPAP?

   Yes No

   More than 5 infants per month? __
   More than 10 infants per month? __

4. What nasal apparatus is most often used for VLBW nasal CPAP in your center?

Short nasal prongs	Brand
Long nasal prongs	Brand
Nasopharygeal tube	Brand
Nasal mask	Brand
Other	Brand

5. For VLBW infants receiving CPAP, does CPAP typically begin in the delivery room?

   Yes No

6. Roughly how many VLBW infants per month have nasal or mask begun in the delivery room and continued in the NICU?

7. Please rank, from most to least common, the indications for CPAP in your nursery:

   Management of RDS
   Management of apnea
   Management of the post-extubation period
   Other, explain _____

8. What device is most commonly used for delivering CPAP pressure in your center (choose one)?

   "Home made" underwater seal — Humidified?
   Other underwater seal — Humidified?
   Commercial CPAP device — Humidified?
   List brand and model
   Ventilator — Humidified?
   List brand and model

9. Is CPAP commonly used for more than 3 days in an individual VLBW infant?

   Yes No

10. Are VLBW infants in your center fed while receiving CPAP?

    Yes No

11. Does your center routinely use an indwelling nasogastric tube in infants receiving nasal CPAP?

    Yes No

12. Please provide <u>any comments</u> that you think might be helpful in planning the SUPPORT training – for example, related to such things as factors important to the success of CPAP, problems that you encounter frequently (nasal erosions, prongs falling out, bleeding, adequate seal, plugging), keeping the mouth closed, actually delivering the preset pressure, etc. etc.

Thanks very much for your help. Return questionnaires to Betty Hastings by Friday June 11, 2004.

From:	Neil Finer
To:	"Poole, W. Kenneth"
Cc:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"; "Michele"
Subject:	RE: SUPPORT
Date:	Monday, June 07, 2004 12:45:17 PM

Sounds like we move ahead with randomization per baby/family and leave it there.
Thanks Ken

-----Original Message-----
From: Poole, W. Kenneth [mailto:poo@rti.org]
Sent: Monday, June 07, 2004 7:00 AM
To: 'nfiner@ucsd.edu'
Subject: RE: SUPPORT

Neil,

We saw in the pilot that things can get out of whack using this method. On top of that it introduces logistical issues concerning the number and types of oximeters centers will have to maintain in order to ensure uninterrupted randomization. Last but not least, it introduces a complexity in the analytic techniques that is necessary to "adjust" for the clustering effect. One can no longer dump the data into SAS or SPSS and get the correct analysis. All of these things argue for a simpler method.

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, June 04, 2004 3:56 PM
To: 'Poole, W. Kenneth'
Cc: Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; higginsr@mail.nih.gov; Neil Finer; 'Wade Rich'; 'Michele'
Subject: RE: SUPPORT

Thanks Ken
The Vent group has at present decided not to randomize by center by week for fear of imbalance even though the coordinators would favor that method. Do you have any thoughts on how we could deal with this, or do you agree that this method is too risky?
Regards
Neil

-----Original Message-----
From: Poole, W. Kenneth [mailto:poo@rti.org]
Sent: Friday, June 04, 2004 12:13 PM
To: 'nfiner@ucsd.edu'
Subject: SUPPORT

Neil,

Looks like I forgot the last paragraph in the Sample Size section in the last attachment. Sorry about that. <<Sample Size Revision2.doc>>

From:	Neil Finer
To:	Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Donovan, Edward (DONOVAEF); Avroy A. Fanaroff, M.D.; Higgins, Rosemary (NIH/NICHD); Wade Rich; Michele Walsh
Subject:	SUPPORT Call
Date:	Thursday, June 10, 2004 12:55:08 AM
Attachments:	SUPPORT Trial June 8 2004.doc

Hi Everyone
Here is the most current version. I have tried to ensure that is clean and current.
I would like to discuss the following tomorrow:
1. The agenda for the Steering Committee
2. The PO Pilots
3. The secondaries
4. The data forms
5.The plans for the Cincinnati in-service in September
6. Some details - randomization, PDA, Shock etc
7. Anything you want to add

Be well
Neil

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 of the NICHD Neonatal Research Network

June 8, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

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 ≥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 COT 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 a 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 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 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 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

Gestation-specific, stratified. Randomization 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 1 hour 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 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) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

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.

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 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.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

An intubated Surfactant-Control infant **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 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 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to attempt to extubate an infant meeting all of the above 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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

OR

- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

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 for 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic/early surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days of age.

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 gradually 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 following NICU admission, with a maximal allowable delay of 120 minutes.** 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% and 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

.

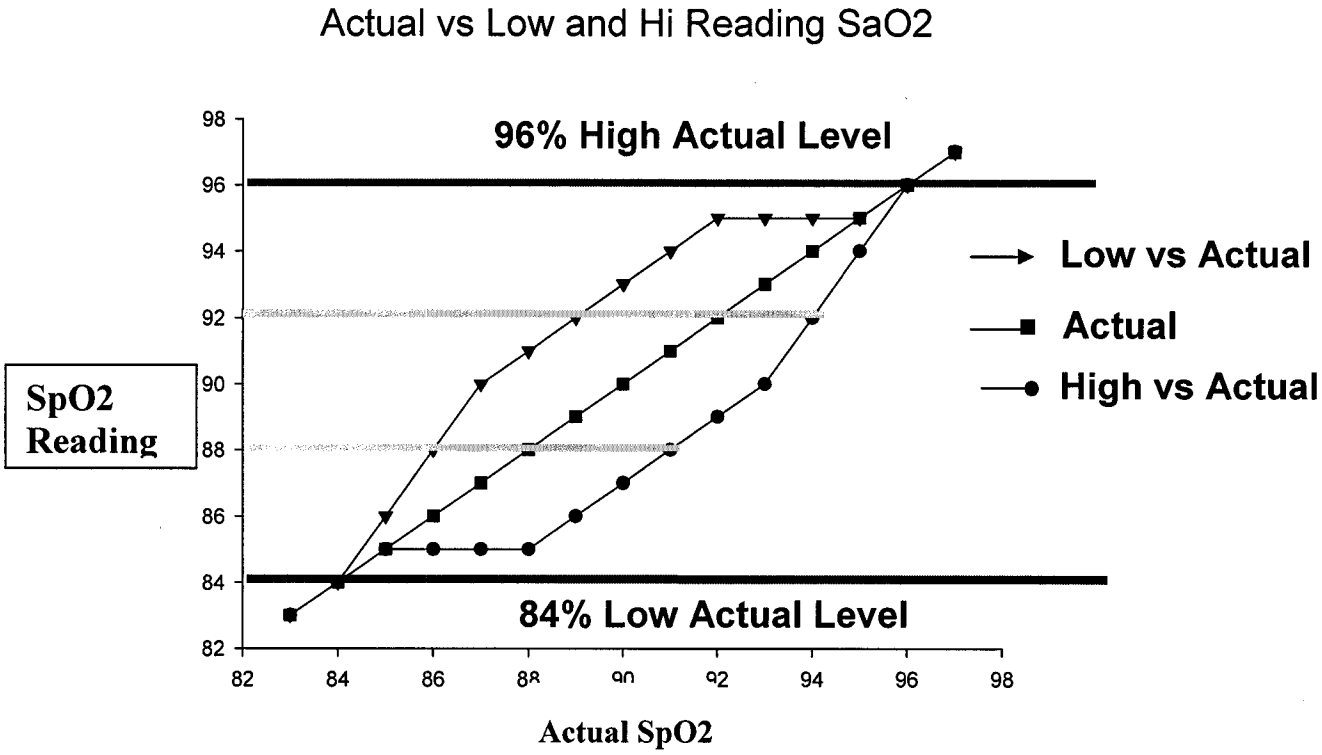
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target Range	Actual Target Range	Alarm Limits
Low SpO2	88-92%	85-89%	85 and 95%
High SpO2	88-92%	91-95%	85 and 95%

In addition, 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. 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 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.

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 or any 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.

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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[60]
4. Death

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, ROP
- 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

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

* 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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes 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
Yes	45	55	50
No	55	45	60
Overall	50	60	55

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

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

		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 infants 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	**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) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Intubate** if both criteria met for >4 hours. • FiO2 > .40 with or without CPAP to maintain an SpO2 > 88% • $PaCO_2$ > 55 torr (art or cap samples), if venous subtract 5 torr from PCO2) **May** intubate for less severe criteria
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) • FiO2 ≤ 50% and SpO2 ≥ 88% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 15 bpm, amplitude < 2X MAP 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 ≤ .40 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 15 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

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Anderson G, Benitz, WE, Madan, A. Retinopathy of prematurity and pulse oximetry: A National Survey of recent practices. J Perinatology 2004;24:164-168

52 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

53 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

54 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

55 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

56 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

57 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

58 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

59 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

60 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From:	Neil Finer
To:	Richard A Polin M.D.
Cc:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"; "Michele"
Date:	Thursday, June 10, 2004 5:42:02 PM

Hi Rich
We have just completed a conference call about the SUPPORT Trial. We would like you and your nurse to speak to our centers representatives on Wednesday Sept 15, in Cincinnati. We would like you to talk about the initiation and maintenance of CPAP in the ELBW infant starting at birth. Ed Donovan is going to Chair and organize this meeting and I have asked him to contact you. I know there will be plenty of questions for you.
We would probably want you there on Tuesday, and Ed will discuss the details with you. I hope that these dates work for you. Thank you for considering this request.
Be well
Neil

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Shahnaz Duara (sduara@miami.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); Michele Walsh (mcw3@cwru.edu); M. D. Avroy A. Fanaroff (aaf2@cwru.edu)
Cc:	Hastings, Betty J.; Petrie, Carolyn; Roberts, Sarah (NIH/NICHD)
Subject:	SUPPORT meeting 7am, Mon Jun 21
Date:	Tuesday, June 15, 2004 12:37:51 PM

To the SUPPORT subcommittee:

There will be a SUPPORT subcommittee meeting at 7am on Monday June 21 at 6100 Executive Blvd, 5th Floor conference room. This meeting is in preparation for the larger 2 hour meeting later in the day.

Please let me know if you are unable to attend.

Thank you,

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Neil Finer
To:	"Duara, Shahnaz"
Cc:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"; "Michele"
Subject:	RE:
Date:	Tuesday, June 15, 2004 3:03:04 PM

Rose thought that we go over to her offices early and have a room there. I will let Rose orchestrate. Thanks Shahnaz

> -----Original Message-----
> **From:** Duara, Shahnaz [mailto:SDuara@med.miami.edu]
> **Sent:** Tuesday, June 15, 2004 10:36 AM
> **To:** nfiner@ucsd.edu
> **Subject:** RE:
>
> Yes - where would we meet?
> Shahnaz
>
> > -----Original Message-----
> > **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> > **Sent:** Tuesday, June 15, 2004 12:26 PM
> > **To:** Duara, Shahnaz; Avroy A. Fanaroff, M.D.; Ed Donovan; higginsr@mail.nih.gov; Neil Finer; 'Wade Rich'; 'Michele'
> > **Subject:**
> >
> > I had a talk with Rose this AM. Would you be willing to meet at 7:00 AM on Monday AM for a brief breakfast meeting to discuss stopping rules and a few small points before we meet with the larger group in DC?
> > Thanks for considering this
> > Be well
> > Neil

From: Neil Finer
To: Petrie, Carolyn; "Duara, Shahnaz"; "Edward Donovan"; wcarlo@peds.uab.edu; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; Hastings, Betty J.; wrich@ucsd.edu
Cc: Petrie, Carolyn
Subject: Re: Early SUPPORT meeting
Date: Thursday, June 17, 2004 11:16:29 AM

Hi Everyone
Another option is to meet at the hotel at 7:00 in the lobby. We would waste less time. We could sit there and work with coffee etc and then leave at 8:00. I will check my email or with Wade as I am about to get on a plane. If you are OK with this let me and Wade know and we can get together at the hotel at around 7:00. I will still be going to Starbuchs at about 6:20. If any one wants to join me, I'm buying.
See you there.
Neil

----- Original Message -----
From: Petrie, Carolyn
To: 'M. D. Neil Finer (nfiner@ucsd.edu)' ; 'Duara, Shahnaz' ; 'Edward Donovan' ; 'M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu)' ; aRose Higgins (higginsr@mail.nih.gov) ; Poole, W. Kenneth ; Hastings, Betty J. ; Wade Rich (wrich@ucsd.edu)
Cc: Petrie, Carolyn
Sent: Thursday, June 17, 2004 6:49 AM
Subject: Early SUPPORT meeting

Since the first SUPPORT meeting start at 7am at NICHD, a couple of services will not be available.

1. 7:30am is the earliest our caterers can deliver the morning snacks/coffee and the coffee bar at the hotel does not open until 7am. There are a couple of Starbucks in the area or room service is available.

2. The shuttle will not be available however there are cabs available just outside the hotel.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Hastings, Betty J.
To:	Carl D"Angio MD (carl_dangio@urmc.rochester.edu); Benjamin, Danny, MD; M. D. Mike Cotten (cotte010@mc.duke.edu); Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; "M. D Kurt Schibler (kurt.schibler@cchmc.org)"; M. D. Susan Hintz (srhintz@stanford.edu); " (RSchelonka@peds.uab.edu)"; M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Brenda Poindexter (bpoindex@iupui.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Abbot Laptook (alaptook@wihri.org); M. D. Avroy A. Fanaroff (aaf2@po.cwru.edu); M. D. Barbara J. Stoll (barbara_stoll@oz.ped.emory.edu); M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. MPH Michael O"Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ron Goldberg (goldb008@mc.duke.edu); M. D. Seetha Shankaran (sshankar@med.wayne.edu); M. D. Shahnaz Duara (sduara@miami.edu); Walid Salhab, MD; Charles Rosenfield, MD; M.D. William Oh; Michele Walsh, MD; Ruth Everett (Reverett@med.miami.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia E McDavid; Kathy Auten (auten002@mc.duke.edu); Linda Reubens (linda_reubens@urmc.rochester.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); Nancy Miller (Nancy.Miller@UTSouthwestern.edu); Nancy Newman; Nancy Peters (npeters@wfubmc.edu); Pat Gettner (pat.gettner@yale.edu); RNC Kathy Arnell (kathy.arnell@sharp.com); Wade Rich; Cathy Grisby(grisbyca@email.uc.edu); Rebecca Bara; Barbara Alexander (balexanba@hotmail.com); Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc:	Petrie, Carolyn
Subject:	SUPPORT Protocol
Date:	Friday, June 18, 2004 9:53:15 AM
Attachments:	SUPPORT Trial June 16 2004 - Final.doc

Attached is the latest version of the SUPPORT Protocol dated June 16, 2004. Please bring a copy of this protocol for the Monday meeting. In case I have missed sending this to everyone attending, please pass this along to any other individual attending from your center. Thanks.

Betty

<<SUPPORT Trial June 16 2004 - Final.doc>>

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

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
June 16, 2004

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants, and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation [8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth.[11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done."[13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those ≥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 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 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 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

Gestation-specific, stratified. Randomization 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 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) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

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.

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 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.

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.
The criteria for Re-intubation are the same as those for Intubation for the CPAP infants;

Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

An intubated Surfactant-Control infant **MUST** have Extubation attempted within 24 hours

of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 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 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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours within the first 14 days of life **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

OR

- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

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 for all infants.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic/early surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days intubation should be performed.
Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days of age.

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 gradually 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 following NICU admission, with a maximal allowable delay of 120 minutes.** 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% and 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

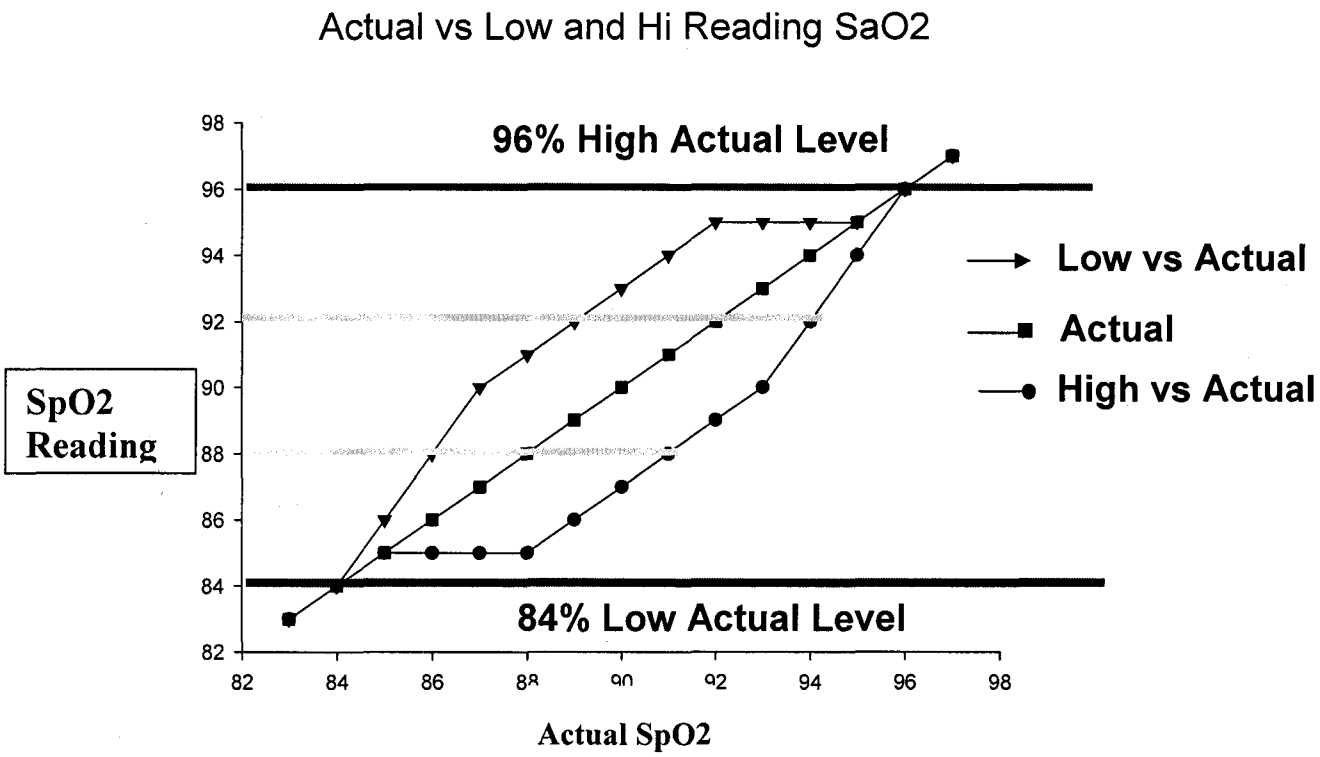
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target Range	Actual Target Range	Alarm Limits
Low SpO2	88-92%	85-89%	85 and 95%
High SpO2	88-92%	91-95%	85 and 95%

In addition, 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 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.

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 or any 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.

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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[60]
4. Death

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
- 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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

* 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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, which includes a 17% attrition factor based on GDB data. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes were calculated from the GDB:

--BPD/Mortality—67%
--ROP ≥ 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
Yes	45	55	50
No	55	45	60
Overall	50	60	55

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

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

SpO2

CPAP	Low	High	Overall
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

CPAP	Low	High	Overall
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	**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) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Intubate** if both criteria met for >4 hours. • FiO2 > .40 with or without CPAP to maintain an SpO2 > 88% • $PaCO_2$ > 55 torr (art or cap samples), if venous subtract 5 torr from PCO2) **May** intubate for less severe criteria
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) • FiO2 ≤ 50% and SpO2 ≥ 88% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 15 bpm, amplitude < 2X MAP 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 ≤ .40 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 15 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

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Anderson G, Benitz, WE, Madan, A. Retinopathy of prematurity and pulse oximetry: A National Survey of recent practices. J Perinatology 2004;24:164-168

52 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

53 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

54 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

55 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

56 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

57 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

58 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

59 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

60 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Protocol
Date: Friday, June 18, 2004 9:59:56 AM

Thanks.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 18, 2004 9:59 AM
To: 'Hastings, Betty J.'
Subject: RE: SUPPORT Protocol

Betty
We will have some copies available -
Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, June 18, 2004 9:53 AM
To: Carl D'Angio MD (carl_dangio@urmc.rochester.edu); Benjamin, Danny, MD; M. D. Mike Cotten (cotte010@mc.duke.edu); Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; 'M. D Kurt Schibler (kurt.schibler@cchmc.org)'; M. D. Susan Hintz (srhintz@stanford.edu); ' (RSchelonka@peds.uab.edu)'; M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Brenda Poindexter (bpoindex@iupui.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Abbot Laptook (alaptook@wihri.org); M. D. Avroy A. Fanaroff (aaf2@po.cwru.edu); M. D. Barbara J. Stoll (barbara_stoll@oz.ped.emory.edu); M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. MPH Michael O'Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ron Goldberg (goldb008@mc.duke.edu); M. D. Seetha Shankaran (sshankar@med.wayne.edu); M. D. Shahnaz Duara (sduara@miami.edu); Walid Salhab, MD; Charles Rosenfield, MD; M.D. William Oh; Michele Walsh, MD; Ruth Everett (Reverett@med.miami.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia E McDavid; Kathy Auten (auten002@mc.duke.edu); Linda Reubens (linda_reubens@urmc.rochester.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); Nancy Miller (Nancy.Miller@UTSouthwestern.edu); Nancy Newman; Nancy Peters (npeters@wfubmc.edu); Pat Gettner (pat.gettner@yale.edu); RNC Kathy Arnell (kathy.arnell@sharp.com); Wade Rich; Cathy Grisby(grisbyca@email.uc.edu); Rebecca Bara; Barbara Alexander (balexanba@hotmail.com); Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc: Petrie, Carolyn
Subject: SUPPORT Protocol

Attached is the latest version of the SUPPORT Protocol dated June 16, 2004. Please bring a copy of this protocol for the Monday meeting. In case I have missed sending this to everyone attending, please pass this along to any other individual attending from your center. Thanks.

Betty

<<SUPPORT Trial June 16 2004 - Final.doc>>
Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

From:	Hastings, Betty J.
To:	M. D. Neil Finer (nfiner@ucsd.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Shahnaz Duara (sduara@miami.edu); Wade Rich (wrich@ucsd.edu); Ruth Everett (Reverett@med.miami.edu); Monica Collins (mcollins@peds.uab.edu); Cathy Grisby (grisbyca@email.uc.edu); Nancy Newman; M. D. Michele Walsh (mcw3@cwru.edu); M. D. Avroy A. Fanaroff (aaf2@po.cwru.edu)
Cc:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; Das, Abhik; Petrie, Carolyn
Subject:	Draft SUPPORT Forms
Date:	Friday, June 18, 2004 11:20:47 AM
Attachments:	SUPP07Intub_extub[6-17-04].doc SUPP02EligibilityForm[6-17-04].doc SUPP03DeliveryForm[6-17-04].doc SUPP04Admissionto NICU Form[6-17-04].doc SUPP05SafetyMonitor[6-17-04].doc SUPP06 Prot Dev[6-17-04].doc SUPP01Screening Log[6-17-04].doc

---

Attached are the "Draft" forms for the SUPPORT Trial. If time permits, we would like to review these at the meeting next week. Thanks.

Betty
<<SUPP07Intub_extub[6-17-04].doc>> <<SUPP02EligibilityForm[6-17-04].doc>>
<<SUPP03DeliveryForm[6-17-04].doc>> <<SUPP04Admissionto NICU Form[6-17-04].doc>>
<<SUPP05SafetyMonitor[6-17-04].doc>> <<SUPP06 Prot Dev[6-17-04].doc>> <<SUPP01Screening Log[6-17-04].doc>>

Betty Hastings

RTI International
Statistic Research Division
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Telephone: (919) 485-7740
Fax: (919) 485-7762
bkh@rti.org

NICU Network

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

SUPP01 Rel 1.0
June 17, 2004

Draft Screening Log

Center: ___ ___ **Site:** ___

Mothers deemed to be at risk of premature delivery at27 6/7 weeks or less should be entered on this form

< This section to be filled out when potential infant identified > <This section to be filled out when the infant is born>

Mother's Last Name	Mother's Hospital Number	Gestational Age (wks/days)	Last Date Eligible (Month/Day/Year)	Consent (Y/N)	Date of Birth (Month/Day/Year)	Enrolled in study Y/N	Network Number	Comments
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	
		__ __ __	__ __/__ __/__ __ __ __	___	__ __/__ __/__ __ __ __	___	__ __ __ __ __ __	

<

A. INCLUSION CRITERIA

1. Inborn infant with a minimal gestational age of 24 weeks 0 days to 27 6/7 completed weeks by best obstetrical estimate? Y N
2. Infant to receive full resuscitation as necessary? Y N
3. Infant does not have known major congenital malformations? Y N

If any of above questions are answered 'N' infant is NOT eligible.

B. EXCLUSION CRITERIA

1. The infant was transported to the center after delivery? Y N
2. The infant was born during a time when the research apparatus/study personnel are not available? Y N

C. CONSENT

1. Consent Status: ___

0 = Not eligible	**4** = Consent not requested
1 = Consent granted	**5** = Physician refused consent
2 = Parent unavailable	
3 = Parent refused consent	

a. **If parent refused consent (3), consent not requested (4) or physician refused consent (5), indicate reason**:

_____

_____

D. RANDOMIZATION

1. Was infant randomized into the study? Y N

a. If **No**, indicate reason(s):_____

_____

b. If Yes, Randomization Number: __ __ __ __

c. Date: __ __/__ __/__ __ __ __ (Month Day Year) d. Time: __ __: __ __ (Hour Min)

Initials of person completing this form: __ __ __

NICU Network

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

SUPP03 Rel 1.0
June 17, 2004

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

A. DELIVERY ROOM INFORMATION

1. Date and time of delivery:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

2. Was CPAP initiated in the DR? Y N

   If Yes, Date and time of CPAP initiation:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

   c. Device: ___

1= T- Piece (Neopuff or other) Specify	2= Ventilator	3= Anesthesia Bag	4 = Bubble	5= Other

   i) If (1) Other (specify the type) _____

   ii) If (5) Other (specify the type) _____

3. Was positive pressure ventilation (PPV) initiated in the DR? Y N

   If Yes,

   a. Duration of PPV: __ __ (Min) __ __ (Sec)

4. Was PEEP used in the DR? Y N

   If Yes,

   a. Level __ __

5. Was infant intubated in the DR? Y N

   a. If Yes, was the intubation successful? Y N

   If Yes, Date and time of intubation:

   b. Date: __ __/__ __/__ __ __ __ (Month Day Year) c. Time: __ __: __ __ (Hour Min)

6. Indication for Intubation: ___

1= Surfactant administration	2= Resuscitation	3= Other

   If (2) Resuscitation,

   a. Low HR? Y Y

   b. Poor color? Y Y

   c. Other (specify):_____ Y Y

7. Did the infant receive surfactant in the DR? Y N

   If Yes, Date and time of administration:

   a. Date: __ __/__ __/__ __ __ __ (Month Day Year) b. Time: __ __: __ __ (Hour Min)

   c. Type: ___

1. Infasurf	2. Curosurf	3. Survanta	4. Exosurf	5. Other (Specify) _____

8. Was active resuscitation required? Y N

   If Yes,

   a. Compressions? Y N

   If Yes,

   1. Duration: __ __ Min

   b. EPI? Y N

   If Yes,

   1. Number of doses: __ __

9. Status at Delivery: ___

1=Admitted to NICU for further care
2=Infant Died

Initials of person completing this form: __ __ __

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= CPAP	2= CV	3= HFV	4= NC	5= RA

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. Was a study oximeter placed on this infant within 2 hours of admission? Y N

   If Yes,

   a. Date: __/__/__ (Month Day Year) b. Time: __:__ (Hour Min)

   c. Serial number: _____

B. NICU PROCEDURES

1. Was the infant intubated for the first time after admission to the NICU within the first 14 days? 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 for 2 successive gases? 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 prior to intubation? Y N

      If Yes,

      a. Date: __/__/__ (Month Day Year) b. Time: __:__ (Hour Min)

      c. Source ___

1- Arterial	2= Venous	3= Capillary

      d. pH ___

      e. pCO2 ___

      f. pO2 ___

      g. FiO2 ___

   3. Was Surfactant given in the NICU? Y N

      If Yes,

a) Dose#	b) Date (Month Day Year)	c) Time: (Hour Min)	d) Type
1	__/__/__	__:__	___
2	__/__/__	__:__	___
3	__/__/__	__:__	___
4	__/__/__	__:__	___

1. Infasurf	2. Curosurf	3. Survanta	4. Exosurf	5. 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

DRAFT SAFETY MONITORING FORM

SUPP05 Rel 1.0
June 17, 2004

Center: __ __ Site No: ___ Network No: __ __ __ __ Birth No: ___ Mother's Initials: __ __ __ Study Day: __ __ Date: __ __ / __ __ / __ __ __ __

Complete a form each day starting with Study Day 1 until Study Day 10 or outcome status, whichever comes first.
Note: Study Day 1 is the day of randomization and is based on the calendar day (00:01 - 24:00).

COMPLETE SECTION A. IF INTUBATED/CPAP (RECORD THE GAS CLOSEST TO THE SCHEDULED TIMES).

A. BLOOD GAS INFORMATION: Record blood gas results closest to the Scheduled Time, if available. If no blood gases were measured, enter FiO_2 only.

a. Scheduled Time	b. Time Measured (hour : min)	c. pH	d. CO2	e. PO2	f. FiO_2	Mode of Therapy* __
1. 08 : 00	__ __ : __ __	__ . __	__ __ __	__ __	__ __	__
2. 16 : 00	__ __ : __ __	__ . __	__ __ __	__ __	__ __	__
3. 24 : 00	__ __ : __ __	__ . __	__ __ __	__ __	__ __	__

*** 1= HFV 2= CV 3 = SIMV 4= CPAP 5=NSIMV**

COMPLETE SECTION B. ONLY IF ON SUPPLEMENTAL OXYGEN BY HOOD OR CANNULA (RECORD FiO_2 ONCE A DAY CLOSEST TO NOON).

B. SUPPLEMENTAL OXYGEN INFORMATION:
Record results closest to noon, if available.

a. Scheduled Time	b. Time Measured (hour : min)	c. FiO_2	d. Flow Rate
1. 12 : 00 (Noon)	__ __ : __ __	__ . __ __	__ __ __

C. INTUBATED/EXTUBATED INFORMATION

1. Was the Infant intubated/extubated on this day? Y N

   If Yes, select one: (If both, use additional form for this day for second event __

   1= Intubation 2= Extubation

   a. At the time of Intubation/Extubation record :
      1. FiO_2 __ __
      2. PCO_2 __ __
      3. Saturation __ __ __

2. Did the infant have any of the following?
   a. Apnea? Y N
   b. Sepsis/R/O Sepsis? Y N
   c. Hemodynamic instability? Y N
   d. Clinically significant PDA? Y N
   e. Other (specify)? Y N

   _____ __

Initials of person completing this form: __ __ __

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

DRAFT PROTOCOL DEVIATION FORM

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

This form should be completed for all randomized patients whenever a protocol deviation is encountered by study personnel. FAX completed form to the DCC at (919) 485-7762.

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. **Duration of intubation for study surfactant administration greater than 1 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. **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
DRAFT Intubation/Extubation Form

SUPP07 Rel 1.0
June 17, 2004

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

Complete this form for all Intubations/ extubations After 14 days

1. Reintubation Number	2. Date of Reintubation Month / Day / Year	3. Reasons for Reintubation:* a. code 1 b. code 2 c. code 3	3) Record FiO_2 and PCO_2 if available: Provide if within 6 hours of procedure		5. Date of Extubation Month / Day / Year
			FiO_2	PCO_2	
1	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
2	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
3	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
4	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
5	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
6	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
7	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
8	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
9	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
10	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
11	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
12	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
13	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
14	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __
15	__ __/__ __/__ __ __ __	___ ___ ___	__	__	__ __/__ __/__ __ __ __

* Reason codes for reintubation

1 = Apnea / hypoventilation
2 = Increased respiratory effort
3 = Sepsis/Possible sepsis
4 = Atelectasis
5 = Elective for procedures
6 = Upper airway abnormality
7 = Other reasons

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: rop secondary to SUPPORT
Date: Sunday, June 20, 2004 9:06:48 PM

I already asked Dale and sent it to her.
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <nfiner@ucsd.edu>
Sent: Thursday, June 17, 2004 10:21 AM
Subject: RE: rop secondary to SUPPORT

> Neil
> I looked this over and have some comments which I will have at the meeting.
> Since we have the expertise, I think it would be good if Dale could give an
> opinion. Is it OK with you if I ask her to do this?
> Thanks
> Rose
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, June 16, 2004 10:13 PM
> To: Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins,
> Rosemary (NIH/NICHD); Neil Finer; 'Wade Rich'; 'Michele'
> Subject: FW: rop secondary to SUPPORT
>
>
> Here is a secondary from Mike Cotton. Please try to look at this and we can
> discuss in DC - After all, we have nothing else to do there!!
> See you Monday bright and early. I'll be walking to Starbucks at 6:20 AM,
> care to join me??
> Be well
> Neil
>
> -----Original Message-----
> From: Michael Cotten [mailto:cotte010@mc.duke.edu]
> Sent: Wednesday, June 16, 2004 1:42 PM
> To: Neil Finer
> Cc: Ronald N Goldberg
> Subject: rop secondary to SUPPORT
>
>
>
>
>
> Neil...here's the second one....along w/ the biosketch and letter of
> support from Dr. Subburaman at Loma Linda who could do IGF-1 levels.
>
>
> mc
>
> (See attached file: rop secondary6.16.04.doc)(See attached file: SM NIH
> Biosketch.doc)(See attached file: Dr. Michael Cotten collaboration

> letter.rtf)
>
>
>
>
>

From:	Neil Finer
To:	Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD); Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Subject:	SUPPORT Trial
Date:	Monday, June 21, 2004 8:42:46 PM
Attachments:	SUPPORT Final Betty June 18.doc

HI All
Here is the next Final protocol
I have added Wally's and Shahnaz's input re steroids, and made a few minor corrections and changed to a single blood gas. By the way this was a request from Alan this morning just before I got up to speak. I thought it was benign so I mentioned it. Hope your OK with this. Sorry for the surprise.
The real word is that we are a go for the visits and training in Cincinnati as planned. We need to consider starting at our 5 sites, and then we can bring up the rest whenever. I suggest we push on getting infants into phototherapy till then. I will start visiting sites in July August as the requests come in.
Please look at the section on steroids. I know that some of us would use hydrocortisone before pressors in view of the results of small randomized trials etc. I look forward to your comments. Ken can you look at the statistics - Seetha was concerned that this section was unclear.
Be well, Travel safe
Neil

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
June 16, 2004

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants, and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation[8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury[9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth.[11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done."[13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those ≥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 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 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 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

Gestation-specific, stratified. Randomization 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 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
- 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.

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 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.

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.

The criteria for Re-intubation are the same as those for Intubation for the CPAP infants;

Re-Intubation Criteria:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

An intubated Surfactant-Control infant **MUST** have Extubation attempted within 24 hours

of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 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 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 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 meeting **BOTH** of these criteria for more than 4 hours within the first 14 days of life **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88% with or without CPAP

OR

- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

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 for all infants.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks

were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic/early surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days intubation should be performed.
Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days of age.

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 gradually 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 following NICU admission, with a maximal allowable delay of 120 minutes.** 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% and 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

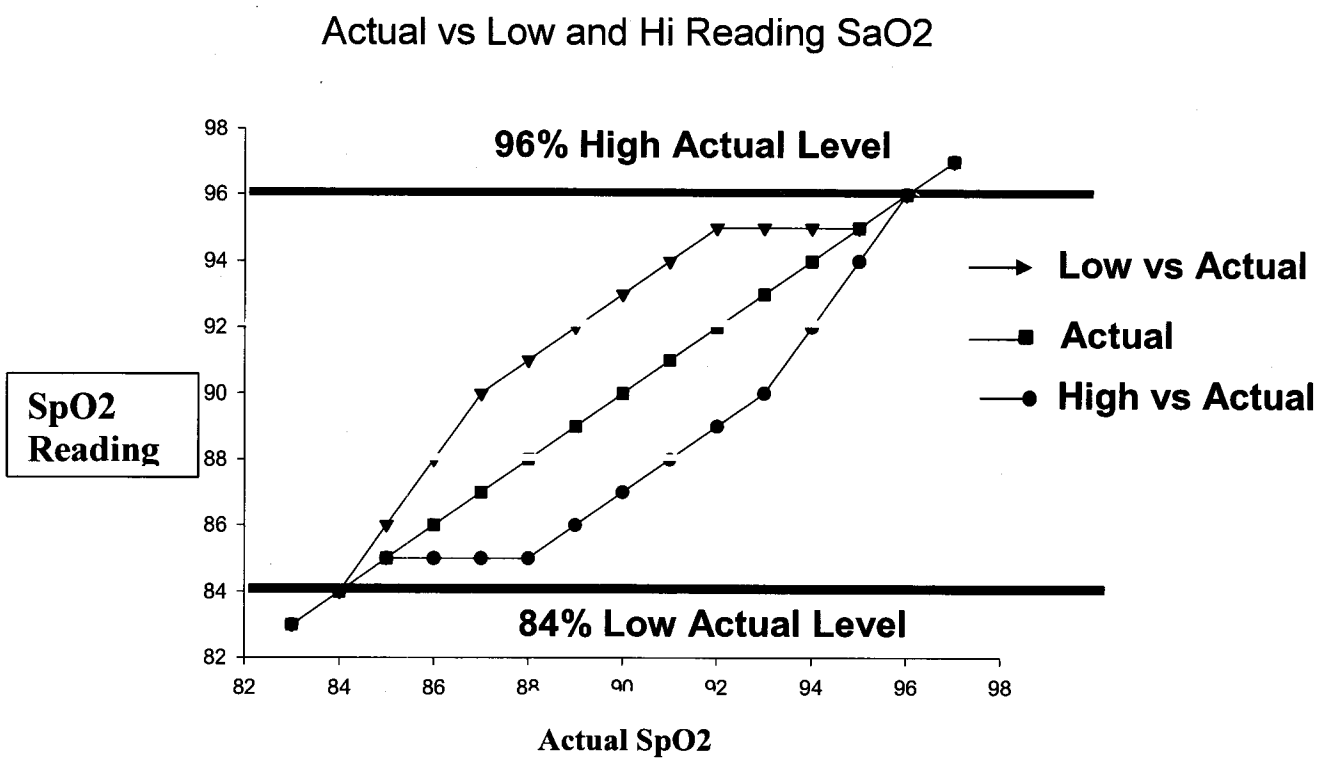
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target Range	Actual Target Range	Alarm Limits
Low SpO2	88-92%	85-89%	85 and 95%
High SpO2	88-92%	91-95%	85 and 95%

In addition, 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 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.

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 or any 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.

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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[60]
4. Death

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
- 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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

* 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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, which includes a 17% attrition factor based on GDB data. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

When sample sizes were estimated for the SUPPORT trial the following base rates for the three outcomes were calculated from the GDB:

--BPD/Mortality—67%
--ROP ≥ 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
Yes	45	55	50
No	55	45	60
Overall	50	60	55

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

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

		SpO2		
		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	**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) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Intubate** if both criteria met for >4 hours. • FiO2 > .40 with or without CPAP to maintain an SpO2 > 88% • $PaCO_2$ > 55 torr (art or cap samples), if venous subtract 5 torr from PCO2) **May** intubate for less severe criteria
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) • FiO2 ≤ 50% and SpO2 ≥ 88% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate ≤ 15 bpm, amplitude < 2X MAP 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 ≤ .40 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 15 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

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Anderson G, Benitz, WE, Madan, A. Retinopathy of prematurity and pulse oximetry: A National Survey of recent practices. J Perinatology 2004;24:164-168

52 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

53 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

54 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

55 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

56 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

57 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

58 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

59 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

60 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Charles Rosenfeld (crosen@mednet.swmed.edu); Poole, W. Kenneth; M. D. Abbot Laptook (alaptook@WIHRI.org); M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Avroy A. Fanaroff (aaf2@cwru.edu); [SCRN] Stoll, Barbara; M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. Michael O"Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ronald Goldberg (goldb008@mc.duke.edu); M. D. Shahnaz Duara (sduara@miami.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Walid A. Salhab (Walid.Salhab@UTsouthwestern.edu); Michele Walsh (mcw3@cwru.edu); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Cathy Grisby (Cinn) (grisbyca@email.uc.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); Gerry Muran (ae5357@wayne.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); (Nancy.Miller@UTSouthwestern.edu); Nancy Newman (nxs5@cwru.edu); Pat Gettner (pat.gettner@yale.edu); RN Kathy Auten (auten002@mc.duke.edu); RN Linda Reubens (linda_reubens@urmc.rochester.edu); Renee Bridge (rbridge@ucsd.edu); RN Nancy Peters (npeters@wfubmc.edu); Ruth Everett (reverett@med.miami.edu); Wade Rich (wrich@ucsd.edu); (vineet.bhandari@yale.edu); Vivek Narendran (Vivek.Narendran@cchmc.org); Krisa Van Meurs (vanmeurs@leland.stanford.edu); Brenda Morris MD (Brenda.H.Morris@uth.tmc.edu); Susie Buchter (susie.buchter@oz.ped.emory.edu); (nirupama_laroia@urmc.rochester.edu); Mike Cotten (cotte010@mc.duke.edu)
Cc:	Hastings, Betty J.; Das, Abhik; Petrie, Carolyn; "Estelle Fischer"; Higgins, Rosemary (NIH/NICHD)
Subject:	SUPPORT Training Participants list
Date:	Thursday, June 24, 2004 4:35:20 PM
Attachments:	SUPPORT Training Participants List v6_24_04.doc

Please review the SUPPORT Training Participants list attached to this email. I made a few minor changes so please let me know ASAP if you have any concerns.

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

SUPPORT Training
Cincinnati, OH

September 14 and 15, 2004

Texas-Houston
Dr. Brenda Morris, Georgia McDavid

Texas-Dallas
Dr. Walid Salhab, James Allen, Gaynelle Hensley, Della Feeha

Miami
Dr. Shahnaz Duara, Ruth Everett, Lucille Fasone, Janet Mitchell

Brown
Dr. Abbot Laptook, Angelita Hensman, Daniel Gingras, Kim Francis

Cincinnati
Dr. Vivek Narendran, Cathy Grisby

Yale
Dr. Vineet Bhandari, Pat Gettner, Tim Mack, Monica Konstantino

Stanford
Dr. Krisa Van Meurs, Bethany Ball, Dan Proud

Alabama
Dr. Wally Carlo, Monica Collins, Robert Johnson

RTI
Dr. Ken Poole, Betty Hastings, Carolyn Petrie

NICHD
Dr. Rosemary Higgins

SUPPORT Training

Cincinnati, OH

September 15 and 16, 2004

Case Western
Dr. Michele Walsh, Nancy Newman, Mike Tracey, Bonnie Siner

Wayne St
Dr. Seetha Shankaran, Rebecca Bara, George Benvenuto, Rontriece Turner

Emory
Dr. Susie Buchter, Ellen Hale

Indiana
Dr. James Lemons, Lucy Miller

Wake Forest
Dr. T. Michael O'Shea, Nancy Peters

Rochester
Dr. Nirupama Laroia, Linda Reubens

Duke
Dr. C. Michael Cotten Denise Lawson, Kathy Auten, Kathy Foy

San Diego
Dr. Neil Finer, Wade Rich, Renee Bridge, Jim Goodmar

RTI
Dr. Ken Poole, Betty Hastings, Carolyn Petrie

NICHD
Dr. Rosemary Higgins

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; M. D. Shahnaz Duara (sduara@miami.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Avroy A. Fanaroff (aaf2@cwru.edu)
Cc:	Hastings, Betty J.; Wade Rich (wrich@ucsd.edu); Das, Abhik; Petrie, Carolyn
Subject:	SUPPORT stopping Rules
Date:	Friday, June 25, 2004 8:35:19 AM

Please let me know your availably for a SUPPORT conference call Thursday, July 15th. (indicate time zone)

The purpose of the call is to discuss the stopping rules for this trial.

Thank you,

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT trial protocol
Date: Friday, June 25, 2004 1:55:45 PM

Will do Rose. I will wait till we have a final version
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 25, 2004 8:15 AM
To: 'nfiner@ucsd.edu'
Subject: RE: COT trial protocol

Neil
We can provide a copy of the protocol, but it is a hard copy, not an electronic version.
Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, June 25, 2004 10:37 AM
To: 'Lisa Askie'
Cc: Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; 'Wade Rich'; 'Michele'
Subject: RE: COT trial protocol

Hi Lisa
I will send you a full protocol of the SUPPORT trial when it is finalized. I anticipate that will be in 2 - 3 weeks. We are a part of the NICHD Neonatal Research Network and this study is funded from the NICHD. We plan to initiate enrollment in September 2004.
Be well
Neil

-----Original Message-----
From: Lisa Askie [mailto:laskie@cochrane.co.uk]
Sent: Friday, June 25, 2004 3:23 AM
To: 'nfiner@ucsd.edu'
Subject: COT trial protocol

Dear Neil,
I am involved with the planning of POST ROP / BOOST-II in both the UK and Australia. I am also involved in looking at the issues surrounding a potential meta-analysis of all the oxygen saturation trials being planned or undertaken around the globe. Hence, would it be possible for you to please send me the full protocol of your factorial SpO2 targeting trial (called COT?)? Can you also tell me where you are up to in terms of funding, (planned?) start and finish dates for the trial?

Any information you can provide would be greatly appreciated.
Regards,
Lisa

<><><><><><><><><><><><><><><><><><><>
Lisa Askie PhD MPH

NHMRC Sidney Sax Postdoctoral Fellow
PARIS Collaboration Coordinator

UK Cochrane Centre
Summertown Pavilion
Middle Way
Oxford. OX2 7LG. UK.

Phone: + 44 (0)1865 516 300
Direct: + 44 (0)1865 517 621
Fax: + 44 (0)1865 516 311
Mobile: + 44 (0)7879 658 326
Email: laskie@cochrane.co.uk
<><><><><><><><><><><><><><><><><><><><>

From:	Neil Finer
To:	Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; sduara@miami.edu; edward.donovan@chmcc.org; wcarlo@peds.uab.edu; aaf2@cwru.edu
Cc:	Hastings, Betty J.; wrich@ucsd.edu; Das, Abhik; Petrie, Carolyn
Subject:	Re: SUPPORT stopping Rules
Date:	Saturday, June 26, 2004 12:33:49 PM

Carolyn
Can you arrange this call for Monday July 19 at 1:00 PM Eastern time, 10:00 Pacific.
Many thanks
Neil

----- Original Message -----
From: Petrie, Carolyn
To: aRose Higgins (higginsr@mail.nih.gov) ; Poole, W. Kenneth ; M. D. Shahnaz Duara (sduara@miami.edu) ; M. D. Ed Donovan (edward.donovan@chmcc.org) ; M. D. Neil Finer (nfiner@ucsd.edu) ; M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu) ; M. D. Avroy A. Fanaroff (aaf2@cwru.edu)
Cc: Hastings, Betty J. ; Wade Rich (wrich@ucsd.edu) ; Das, Abhik ; Petrie, Carolyn
Sent: Friday, June 25, 2004 5:35 AM
Subject: SUPPORT stopping Rules

Please let me know your availably for a SUPPORT conference call Thursday, July 15th. (indicate time zone)

The purpose of the call is to discuss the stopping rules for this trial.

Thank you,

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Avroy A. Fanaroff
To: Higgins, Rosemary (NIH/NICHD); Dale_Phelps@URMC.Rochester.edu
Cc: nfiner@ucsd.edu
Subject: RE: Revising ROP Coding for GDB
Date: Wednesday, April 07, 2004 5:10:28 PM

Hi
Looks good for a first effort
Dale, looks like you have done these before
See you Wednesday
regards
Av

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

From: Phelps, Dale
Date: 04/07/04 15:30:38
To: 'Avroy A. Fanaroff'; higginsr@mail.nih.gov
Cc: nfiner@ucsd.edu
Subject: RE: Revising ROP Coding for GDB

Hi all,

Here is my first attempt at a flow sheet of what we could most easily derive from the GDB as currently stands. It is a PowerPoint, so open it with that. The first "slide" is for all GDB, the second for those <1 kg which adds the advantage of using the 18 month follow up.

We may not be able to get everything on these "slides" with what we have now.
Also, there may be outcomes we would like to add to this that will require changing the datasheets. (I know I have some for Inositol, and Neil, you'll probably have some for COT).

This gives us something to start with and work on.

Dale

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Wednesday, April 07, 2004 2:49 PM
To: higginsr@mail.nih.gov; Phelps, Dale
Cc: nfiner@ucsd.edu
Subject: Re: Revising ROP Coding for GDB

From:	Neil Finer
To:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"
Cc:	wrich@ucsd.edu; Maynard Rasmussen
Subject:	SUPPORT Trial
Date:	Thursday, April 08, 2004 8:34:12 PM
Attachments:	SUPPORT Trial April 7 04.ppt SUPPORT Trial March 23 final.doc SUPPORT Trial graph Final 04_05.doc

Hi Everyone
Here are the final protocol and a presentation for the combined MFM NRN meeting that Wally will present. We have been looking at ways to evaluate the Hi and Low POs and Wade and Maynard will talk about these at the meeting. In addition, Wally will discuss the study to test the POs for the unblinding, use of the alarm limits and downloads etc. The current methodology of the POs will use an averaging of 12 seconds, an alarm delay of 10 seconds and a further alarm if the SpO2 falls 5% below the low limit (80%). I hope that you will discuss these issues at the Meeting.
Be well and have a great meeting
Neil

NETWORK FEASIBILITY STUDY: DR CPAP

- Conducted in the 5 Network ventilation sites
- Objective : test feasibility of using CPAP at birth as a mode of respiratory support
- n=104; 55 CPAP; 49 CONTROL
- Criteria for feasibility: >90% of randomized infants followed the prescribed protocol

The study did meet the feasibility criteria.

NETWORK FEASIBILITY STUDY: DR CPAP (Pediatrics – In Press)

- 104 infants < 28 weeks enrolled in 6 months.
- All Infants of 23 weeks or less required DR Intubation for resuscitation indications
- Such infants would not be informative in a study evaluating DR CPAP as a primary mode of respiratory support compared with surfactant
- Mode of randomization by center by week led to large imbalance, and will not be used.

Next Trial : SUPPORT

- **Surfactant**
- **Positive airway pressure**
- **Pulse Oximetry**
- **Randomized**
- **Trial**

SUPPORT Trial

- Essentially 2 trials conducted simultaneously on the same population of ELBW infants
- A Factorial design which ensures that there will be an equal number of infants randomized to each of the 4 possible strategies
- Not prospectively powered to evaluate an interaction, but if a large interaction exists, it will be noted

SUPPORT Trial

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
CPAP With Permissive Ventilation	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control with Prophylactic or Early Surfactant	Control + Low SpO2	Control + High SpO2

PRIMARY HYPOTHESIS

- EARLY CPAP AND PERMISSIVE VENTILATORY STRATEGY WILL INCREASE SURVIVAL OF ELBW INFANTS WITHOUT BPD

- LOWER SpO2 (85-89%) WILL INCREASE SURVIVAL WITHOUT SEVERE ROP (THRESHOLD DISEASE OR REQUIRING SURGERY)

SUPPORT: Inclusion Criteria

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

SUPPORT Trial: Exclusion Criteria

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available.
- Infants < 24 weeks 0 days or $\geq$ 28 weeks 0 days, completed weeks of gestation

SUPPORT - Ventilation Arm

- **Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic/early surfactant within 1 hour of delivery**

SUPPORT - Ventilation Arm

- Treatment - CPAP infants will be forced to early extubation attempted at higher ventilation settings
- Control – Surfactant infants will be extubated at more conventional settings

Intubation Criteria: Treatment Group - CPAP

May be intubated for any of following*

- **FiO2 >.50 required to maintain indicated SpO2 ≥ 88% for one hour**
- **Arterial/Cap PaCO2 > 65 (PvCO2 > 70) for 2 successive gases ≥ 15 minutes apart.**
- **Hemodynamic instability Apnea requiring bag and mask ventilation**
- **The occurrence of sepsis, shock or surgery**

*** Minimum criteria, may be exceeded by MD choice**

Extubation Criteria – CPAP Group

Attempt extubation within 24 hours of fulfilling all of the following criteria:

- **Arterial/Cap PCO_2 < 65 torr and pH > 7.20**
- **An $FiO_2 \leq 50\%$ with $SpO_2 \geq 88\%$**
- **Mean airway pressure < 10 cm H_2O, vent rate ≤ 15 bpm, amplitude < 2X MAP if on high frequency ventilation**
- **Absence of clinically significant PDA**
- **Hemodynamically stable**

Extubation Criteria – Surfactant Group

Attempt extubation within 24 hours of fulfilling all of the following criteria

- **Arterial/Cap $PaCO_2$ < 50 torr and pH > 7.30**
- **$FiO_2 \leq .40$ with SpO_2 > 88%**
- **Mean airway pressure < 8 cm H_2O, vent. rate ≤ 15 bpm, amplitude < 2X MAP on high frequency ventilation**
- **Absence of clinically significant PDA**
- **Hemodynamically stable**

Re-Intubation Criteria: Control Group - Surfactant

Intubate if both criteria met for >4 hours.

May intubate for less severe criteria

- **An FiO_2 > .40 with or without CPAP to maintain an SpO_2 < 88%**
- **Arterial/Cap $PaCO_2$ > 55 torr ($PVCO_2$>60)**

OR

- **Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.**

Ventilation Criteria

- **In effect for 14 days for infants of 24 to 25 6/7ths weeks**
- **In effect for 7 days for infants of 26 to 276/7ths weeks**
- **CPAP may be discontinued when in room air > 1 hour**
- **May be restarted at any time in either group**
- **Nasal SIMV to be used only after initial intubation**

Oxygen Saturation Monitoring Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter < 2 hours

SpO2 Targets

SpO2 – 85% - 89%

SpO2 – 91% - 95%

Maintain till off ventilatory support and Oxygen

	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO2 range group	88-92%	85-89%	85-95%	85-94%
High SpO2 range group	88-92%	91-95%	85-95%	86-95 %

Pulse Oximetry Protocol

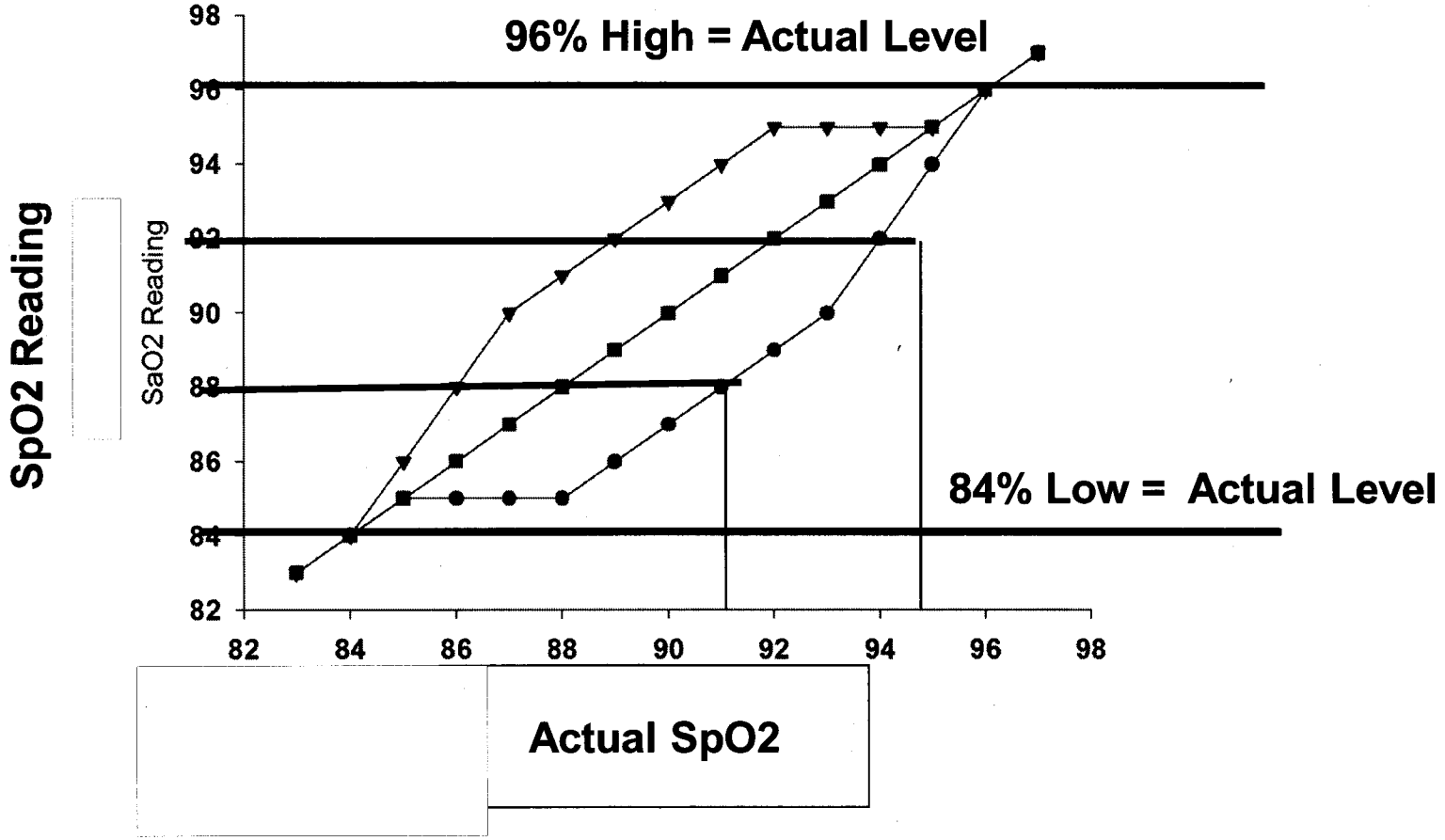
- LOW RANGE: TARGET SpO2 85-89%
- HIGH RANGE: TARGET SpO2 91-95%
- STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE
- STUDY PO'S Display NOT THE ACTUAL SpO2 for values BETWEEN 85% TO 95%

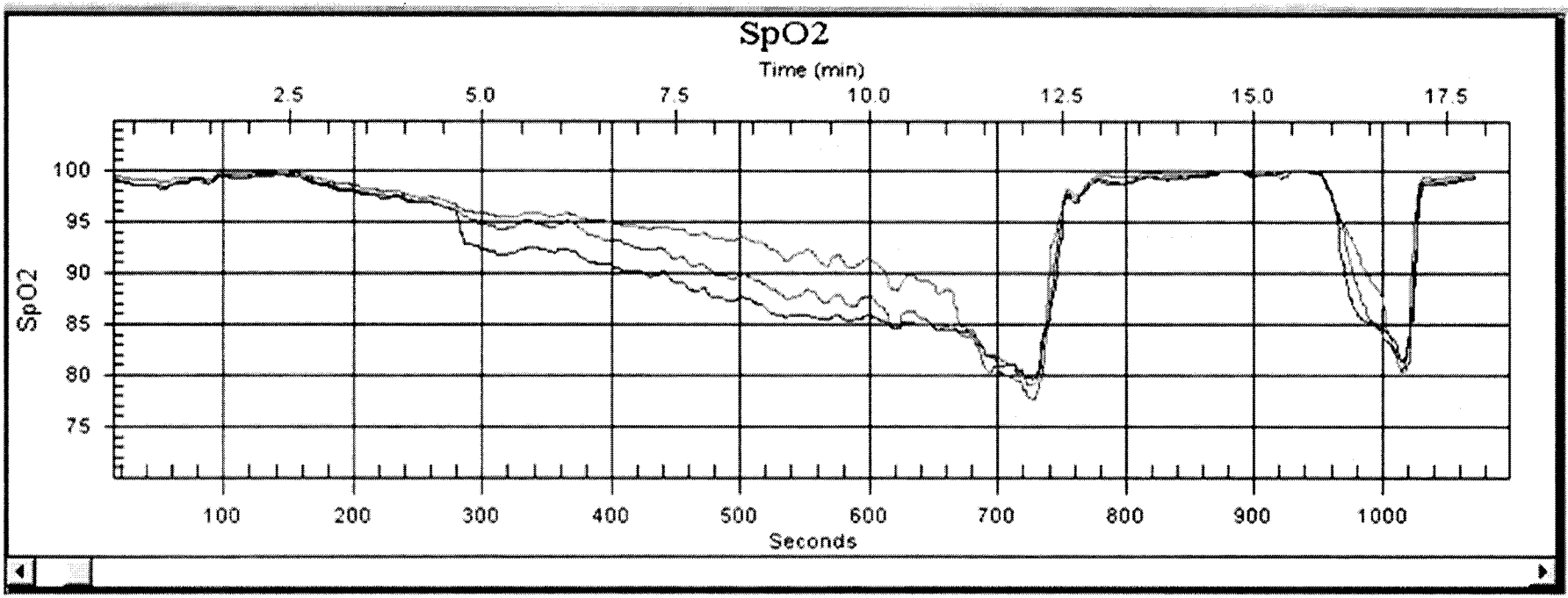
Pulse Oximetry Protocol

- OUTPUT TARGETS AND ALARMS FOR BOTH GROUPS WILL BE SET AT 88-92% AND 85-95% RESPECTIVELY

- SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED

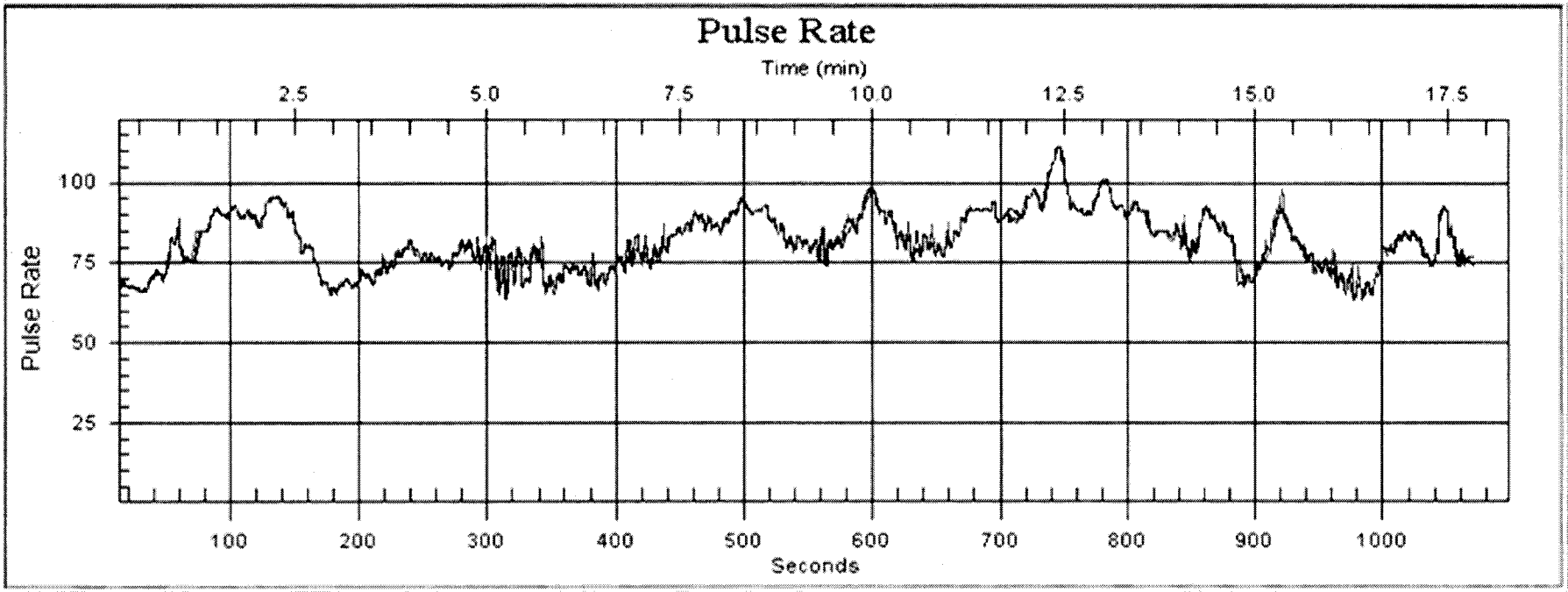
Plot of Actual versus Displayed SpO2





SpO2 Instruments:
REF Radical: SpO2
Low Group : SpO2
High Group : SpO2

SpO2 Comment:



Pulse Rate Instruments:
REF Radical: PR
Low Group : PR
High Group : PR

Pulse Rate Comment:

OXYGENATION PROTOCOL-CONT'D

- **STUDY PO WILL REMAIN WITH INFANT UNTIL OFF OXYGEN**
- **SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER 1-2 WEEKS DURING STUDY**
  - **(We are still determining the minimal need – may be once per month)**

Sample Size Estimate

- The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.
- We will randomize by family, all multiples to same arm – we have made a 12% adjustment to sample size to account for this clustering

Sample Size

- **Postulating a 10% difference in primary outcome a sample size of 1310 infants will provide for 80% power for the primary as well as NDI/Mortality (Secondary Outcome)**
- **Adding 15% attrition factor results in a total of 1506 infants.**

SUPPORT – Time Line

- **Test POs within next 4- 8 weeks at Vent sites**
- **Prepare Study Manual (already started)**
- **Plan in-service, teaching video**
- **Consider need for site visits (?Columbia?- July – August?)**
- **Each site to choose a committed PI**
- **Begin Conference calls with site PIs to review details of Protocol – May – June**
- **Start Enrollment Sept 1 – earlier if possible!**

Group	Early CPAP/Early Extubation	Prophylactic Surfactant
Gestational Age Stratum	24-25 Weeks + 26-27 weeks	24-25 Weeks + 26 – 27 weeks
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. Intubate for NRP guidelines only.	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** If intubated, give **surfactant** within **the first 48 hours** of life in the presence of respiratory distress • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • Arterial/Cap $PaCO_2$ > 65 (PvCO2 > 70) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.	**Reintubation Criteria** Intubate if **both** met for >4 hours. **May** intubate for less severe criteria • An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88% • Arterial/Cap $PaCO_2$ > 55 torr (PVCO2>60) **OR** • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.
Extubation Criteria	Attempt extubation **within 24 hours of** fulfilling **all** of the following criteria: • Arterial/Cap PCO_2 < 65 torr and pH > 7.20 • An FiO2 ≤ 50% with SpO2 ≥ 88% • Mean airway pressure < 10 cm H_2O, vent rate ≤ 15 bpm, amplitude < 2X MAP if on high frequency ventilation • Absence of clinically significant PDA • Hemodynamically stable	Attempt extubation **within 24 hours** of fulfilling **all** of the following criteria • Arterial/Cap $PaCO_2$ < 50 torr and pH > 7.30 • FiO2 ≤ .40 with SpO2 > 88% • Mean airway pressure < 8 cm H_2O, vent. rate ≤ 15 bpm, amplitude < 2X MAP on high frequency ventilation • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surfactant	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
CPAP D/C	In room air for at least 1 hour	
CPAP Restart	At any time	
Duration of Criteria	14 days for 24-25 wk stratum, 7 days for 26-27wk stratum	

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 of the NICHD Neonatal Research Network

Mar 23, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

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 ≥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. 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 COT 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.

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.[51] 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[52] using a 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.[53] 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 of 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.[54] 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 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 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 $\geq$ 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

Neopuff resuscitators, equivalent T-piece resuscitators or a Neonatal ventilator including disposable circuits, will be provided to all sites for delivery room management. Sites may use equivalent devices that are already available. A training video to explain the proper use of the Neopuff® will be provided to each site in advance of a site visit. If available CPAP will be provided by the Bubbleflow device (Fisher&Paykel, Auckland, NZ). This device is currently under FDA consideration. We may apply for an IDE to use this device for this trial if it has not received FDA approval prior to trial initiation

3.7 Randomization

Gestation-specific, stratified. Randomization 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 are being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate randomization to either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and to 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 1 hour 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 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) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 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 14 days of life for 24-25 weeks and 7 days for 26-27 weeks.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

An intubated Surfactant-Control infant **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 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 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to attempt to extubate an infant meeting all of the above 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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

OR

- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

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 for 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic/early surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks.

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 gradually 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 following NICU admission, with a maximal allowable delay of 120 minutes.** 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% to 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

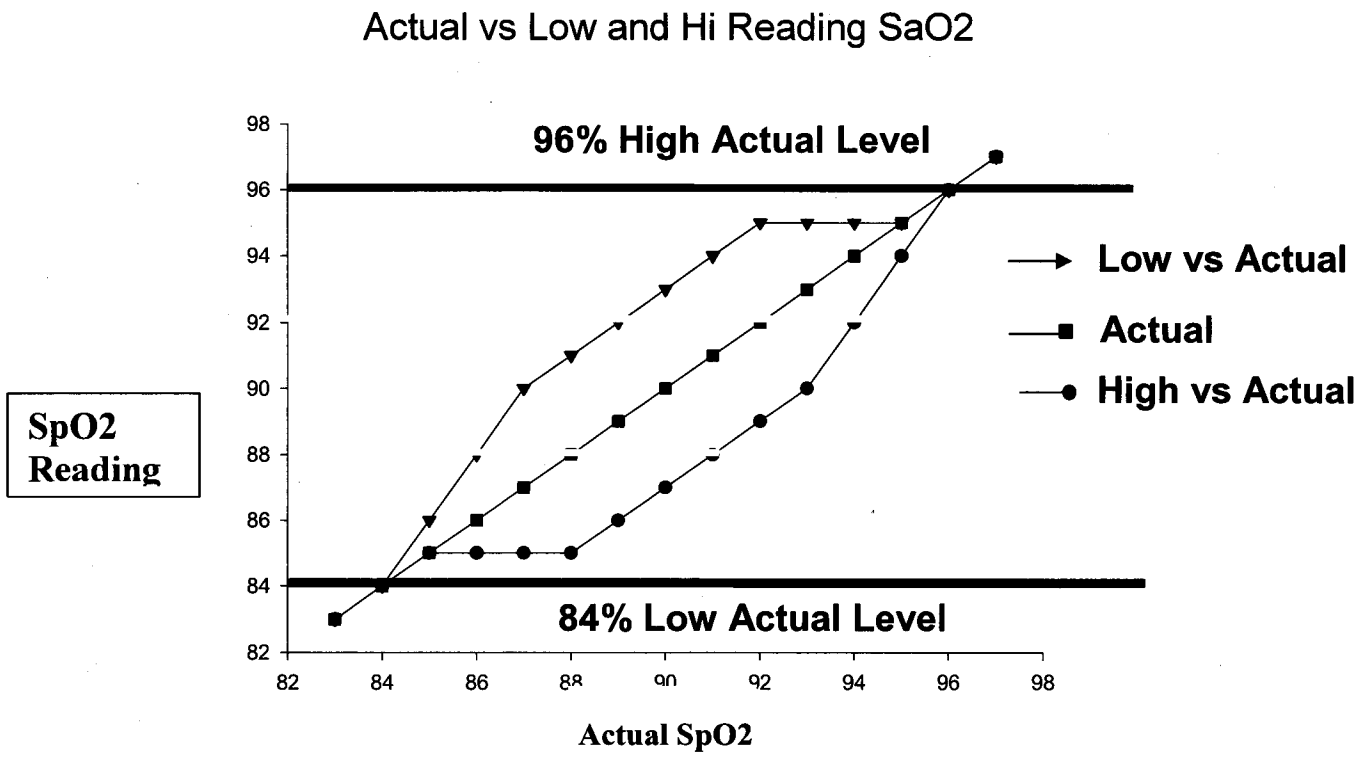
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarm Limits Will alarm above or below these values	Actual Alarm Values
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

In addition, and as an added safety issue, we will be asking the pulse oximeter provider to program the software of the actual pulse oximeters used in this trial to display the actual reading when then the actual 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, ie < 85% and hyperoxia, ie SpO2 > 95%. An infant with an SpO2 outside these limits will have his/her actual SpO2 displayed on their pulse oximeter available for their caretakers to allow appropriate intervention. ***Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values***. We have asked the manufacturer to utilize the averaging algorithm of 16 seconds in keeping with current clinical practice. Some network centers use an averaging interval of 30 seconds. This averaging time will permit the change in reading from the altered readings to the actual SpO2 values without unmasking the caretakers.

We believe that this methodology will reassure all caretakers, and provide an acceptable ethical design for this trial. In addition we are confident that caretakers will not be aware of the shift from altered SpO2s to actual values, as few if any caretakers actually watch the changes in SpO2 but are alerted to do so by alarms. Thus in most circumstances by the time the caretaker responds to an alarm, the change from altered to actual SpO2 will have, in most circumstances, already occurred. 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.


Actual vs Low and Hi Reading SaO2
96% High Actual Level
84% Low Actual Level
Low vs Actual
Actual
High vs Actual
SpO2 Reading
Actual SpO2
98
96
94
92
90
88
86
84
82
82
84
86
88
90
92
94
96
98

Every 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) from the study pulse oximeters will be downloaded and transmitted without further review or analyses 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.

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 device called a "NeoPuff®" or an equivalent device (See **3.6**). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece to allow the resuscitator to set both the Peak Inspiratory Pressure (PIP) and the PEEP or CPAP level, and to control the rate of ventilation. This device can also deliver CPAP.

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.[55][56][57]. 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.[58]

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.

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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[59]
4. Death

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, ROP
- 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

6.1 Training Study Personnel

A training video on the use of the Neopuff or equivalent device, and the set-up and use of the video recording apparatus will be distributed to sites for review before the training site visit. The site visit by the PI and representatives from Fisher-Paykel (distributors of Neopuff) to install the equipment and in-service the Neopuff and the Bubbleflow for CPAP(if available). Training will be provided as well as a detailed protocol for obtaining and transmitting the stored PO SpO2 and Heart rate data.

6.1.1 Job Descriptions of Study Personnel

The NICHD Coordinators will assist the Respiratory therapists in each unit regarding the set up the Neopuff equipment and Bubbleflow apparatus (if utilized for CPAP – currently not FDA approved).

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during a dedicated training meeting. In addition the study staff will have extensive in-service regarding the study POs utilized.

6.1.3 Training Materials and Certification

A training video to review the set-up of the Neopuff, and the bubbleflow will be distributed and sites will be certified on the use of the Neopuff, and bubbleflow apparatus.

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR COT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes 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
Yes	45	55	50
No	55	45	60
Overall	50	60	55

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

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. On site monitoring will be performed by an initial site visit, review of the data forms, and independent review of the video recordings, which contain the entire randomized elements of this study. Protocol violations will be reviewed, and if frequent, will 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 infants 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				

Treatment Group	Early CPAP/Early Extubation	Prophylactic Surfactant
Gestational Age Stratum	24-25 Weeks + 26-27 weeks	24-25 Weeks + 26 – 27 weeks
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** **If intubated, give surfactant within the first 48 hours of life in the presence of respiratory distress** • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • Arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if PvCO2 > 70 torr) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.	**Reintubation Criteria** **Intubate** if both criteria met for >4 hours. **May** intubate for less severe criteria • $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) • An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%
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% • A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV) • 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 ≤ .40 with SpO2 > 88% using the study oximeter • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 15 bpm, amplitude < 2X MAP on high frequency ventilation (HFO) • Absence of clinically significant PDA

Repeated Surfactant Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
CPAP Discontinuation	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Study Criteria in PNAge(days)	14 days	7 days

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

52 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

53 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

54 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

55 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

56 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

57 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

58 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

59 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT call
Date: Tuesday, April 20, 2004 1:02:41 PM

Rose-

I am still waiting to hear from Neil's secretary on his availability for a conference call. Do you know if he is in town (ie his office)?

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; M. D. Neil Finer (nfiner@ucsd.edu); M. D. Shahnaz Duara (sduara@miami.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); Michele Walsh (mcw3@cwru.edu); M. D. Avroy A. Fanaroff (aaf2@cwru.edu)
Cc:	Hastings, Betty J.; Petrie, Carolyn; Das, Abhik; Heidi Squibb (UCSD) (hsquibb@ucsd.edu); Diane Timmer (Cincinnati) (diane.timmer@cchmc.org); Maria V. Valles (Miami) (Mvalles2@med.miami.edu); (mlg@cwru.edu)
Subject:	scheduling SUPPORT conference call
Date:	Tuesday, April 20, 2004 4:12:30 PM

Please send me your availability for a SUPPORT (formerly DRCPAP) conference call:

Tues Apr 27
Thur Apr 29

Thur May 6
Fri May 7

Mon May 10
Tue May 11
Wed May 12
Thur May 13
Fri May 14

Thank you!!!

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT
Date: Wednesday, April 21, 2004 10:56:36 AM

Rose-

Wade wanted to know if he should break the news regarding the 5.2M award for the support trial.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Hastings, Betty J.
To:	Ruth Everett (Reverett@med.miami.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia E McDavid; Gerry Muran (ae5357@wayne.edu); Kathy Auten (auten002@mc.duke.edu); Linda Reubens (linda_reubens@urmc.rochester.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); Nancy Miller (Nancy.Miller@UTSouthwestern.edu); Nancy Newman; Nancy Peters (npeters@wfubmc.edu); Pat Gettner (pat.gettner@yale.edu); RNC Kathy Arnell (kathy.arnell@sharp.com); Wade Rich; Cathy Grisby(grisbyca@email.uc.edu); Barbara Alexander (balexanba@hotmail.com); Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD
Cc:	Auman, Jeanette O.; Petrie, Carolyn; Schaefer, Scott E.; Higgins, Rosemary (NIH/NICHD)
Subject:	SUPPORT Trial
Date:	Wednesday, April 21, 2004 3:43:09 PM
Attachments:	SUPPORT Trial March 23.doc SUPPORT Trial graph 04_05.doc

---

Attached is the current version of the SUPPORT trial and a graph of ventilatory interventions. Wade will give a brief update on this study tomorrow on the coordinators call.

Betty

From:	Petrie, Carolyn
To:	Michele Walsh (mcw3@cwru.edu); Brenda Morris MD (Brenda.H.Morris@uth.tmc.edu); Wade Rich (wrich@ucsd.edu); (Nancy.Miller@UTSouthwestern.edu); Angelita Hensman (ahensman@wihri.org); Bethany Ball (mbball@leland.stanford.edu); Cathy Grisby (Cinn) (grisbyca@email.uc.edu); Ellen Hale (ellen_hale@oz.ped.emory.edu); Gay Hensley (gaynelle.hensley@utsouthwestern.edu); Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); Gerry Muran (ae5357@wayne.edu); Lucy Miller (lucmille@iupui.edu); Monica Collins (mcollins@peds.uab.edu); Nancy Newman (nxs5@cwru.edu); Pat Gettner (pat.gettner@yale.edu); Renee Bridge (rbridge@ucsd.edu); RN Kathy Auten (auten002@mc.duke.edu); RN Linda Reubens (linda_reubens@urmc.rochester.edu); RN Nancy Peters (npeters@wfubmc.edu); Ruth Everett (reverett@med.miami.edu); William Oh2 (WOh@wihri.org); Ken Poole (poo@rti.org); Higgins, Rosemary (NIH/NICHD); M. D. Abbot Laptook (alaptook@WIHRI.org); M. D. Avroy A. Fanaroff (aaf2@cwru.edu); M. D. Barbara J. Stoll (barbara_stoll@oz.ped.emory.edu); M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. Ed Donovan (edward.donovan@chmcc.org); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. Michael O"Shea (moshea@wfubmc.edu); M. D. Neil Finer (nfiner@ucsd.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ronald Goldberg (goldb008@mc.duke.edu); M. D. Shahnaz Duara (sduara@miami.edu); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); M. D. Walid A. Salhab (Walid.Salhab@UTsouthwestern.edu); Seetha Shankaran (sshankar@med.wayne.edu)
Cc:	Higgins, Rosemary (NIH/NICHD); Hastings, Betty J.; Petrie, Carolyn
Subject:	SUPPORT Study PI, RT, Coord
Date:	Thursday, April 22, 2004 1:38:35 PM

I am compiling a SUPPORT Trial directory. Please send me names, phone number and email addresses for the following staff for this study:

1. Study PI
2. Respiratory Therapist
3. Coordinator/Nurse (if different from site coord)
4. Other staff

Thank you for your help!
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Neil Finer
To:	"Wally Carlo, M.D."
Cc:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"
Subject:	RE:
Date:	Wednesday, April 28, 2004 3:22:08 PM
Attachments:	PILOT STUDY OXYGENATION TRIAL IN ELBW INFANTS revised 4 28 04NF.doc

Hi Wally
Thanks for sending this pilot. I have made a number of suggestions and would appreciate everyone's feedback.
I have attached my revised protocol.
Be well
I will hopefully see you next week in SF.
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, April 28, 2004 11:36 AM
To: nfiner@ucsd.edu; aaf2@cwru.edu; sduara@miami.edu; edward.donovan@cchmc.org
Cc: Wally Carlo, M.D.
Subject:

This is a draft of the protocol on oxygen saturation. I would like to get your feed back to discuss this pilot. If there are important changes can discuss them during the conference call. Otherwise I can make the changes suggested by all of you. Thanks for your advise. Wally

Pilot Study for the Oxygenation Trial in Extremely Low Birth Weight Infants

Abstract

Statement of problem

A consensus conference on assisted ventilation concluded that blood gas targets do not have to be in the "normal" ranges. Oxygen saturation targets in infants vary markedly between centers and there is no consensus on the targets. Published acceptable levels of oxygen saturation in neonates range from 85 to 98% or even lower. Keeping saturation targets in the high side of this range may have short term benefits such as prevention of desaturation, vasoconstriction and bronchoconstriction episodes. In addition, in infants with prethreshold retinopathy of prematurity (ROP), progression to threshold ROP may be reduced with higher saturation targets. While there has been concern that low saturations may result in cerebral palsy and that higher saturations may prevent neurodevelopmental impairment, a randomized controlled trial of infants beyond the first month after birth reported that oxygen saturations in the high 90s did not improve long term outcomes. Benefits of targeting low saturations may be a lower incidence of bronchopulmonary dysplasia and retinopathy of prematurity.

A recent randomized controlled trial targeted saturations between 91 to 94% versus 95 to 98% in preterm infants born at less than 30 weeks of gestational age when they had reached a postmenstrual age of 32 weeks. This large randomized controlled trial reported that there was no improved growth or neurodevelopment (blindness, cerebral palsy or developmental quotient) by keeping saturations 95 to 98%. However, targeting high saturations resulted in a longer period of oxygen supplementation after randomization (40 versus 18 days) and a higher dependence on oxygen supplementation at 36 weeks and after discharge. A study to target high saturations in infants with prethreshold ROP showed that there was a decreased progression to threshold ROP but there was a prolongation of oxygen supplementation and hospitalization with a target of higher saturations.

However, these studies have targeted oxygen saturations in infants beyond the first month after birth. It is necessary to determine the desired oxygen targets in infants in the first days of life because lung injury, ROP, and other complications due to high or low oxygen saturations may start early after birth.

The current pilot study will be a short term study to test the feasibility of aiming for two different targets of oxygen saturation, one of which is around the lower limit of current practice in many centers (85 to 89%) and the other on the upper limit (91-95%).

Hypothesis

We hypothesize that relative to infants managed with higher target range (91-95%), the use of a lower SPO_2 (85 to 89%) for 24 hours during the first week after birth will result in an improvement in oxygenation index.

Secondary hypotheses: We hypothesize that relative to infants managed with a higher SPO_2 target (91-95%) for 24 hours during the first week of life, that the use of a lower $SaPO_2$ (85-89%) will result in:

1) lower median saturation by at least 4%

2) no change in $PaCO_2$ or bicarbonate.

3) No unblinding of the caretakers – this will be important if the study is to be successful.

Study subjects will be infants of 24 and 07-27 and 6/7 weeks if they are receiving mechanical ventilation or continuous positive airway pressure. Infants will be stratified into two gestational age strata from 24/7 to 25 6/7 weeks and from 26 0/7 to 27 6/7 week, obtained by best obstetrical estimate.

Inclusion criteria are as follows:

1) 24 0/7 week to 27 6/7 week

2) Infants requiring CPAP (will this work if you postulate an OI change – it is unlikely to be largely affected maximal change will be 1-3 OI points) or mechanical ventilation Should the primary be the saturation difference?

Exclusion criteria are as follows:

1) Infants outside of the gestational age window at birth or beyond the first week after birth

2) Infants whose parents/legal guardians refuse consent

3) Infants born during the time when the research/study personnel are not available.

Rationale/justification

It is still unknown what the optimal $SaPO_2$ targets are for infants during the first week after birth and whether targeting different saturations actually result in distinct ranges of saturations in infants. The approved Continuous Positive Airway Pressure and Oxygenation Trial (COT study) of the NICHD Neonatal Research Network will test whether targeting oxygen saturations for a prolonged period results in improvement in important clinical outcomes. The purpose of this pilot study is to determine if during a 24 hour period, targeting different saturation ranges results in improvement in oxygenation index and to determine if different $SaPO_2$ targets result in different SPO_2 levels in these infants.

Background/previous studies

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and

glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.[i] 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.[iiiiiiv] 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.[v] 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.[vi]

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported that infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.[vii viii] 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.[ix] A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal mortality in infants resuscitated with room air (6 vs 11%, $p<0.005$ or 0.57 (95% CI 0.40 – 0.81))[x]. 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).[xi] 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%).[xii] 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.[xiii] 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.[xiv]

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.[xv] 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.[xvi] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months.

There is a need to determine that the use of altered POs will not lead to inadvertent unblinding, and that the use of common alarm limits will lead to an actual separation of SpO2 values. The entire range of displayed SpO2 values is altered either high or low from 85% to 95%. The maximum difference between the high and low POs will be at the center of the target range, approximately 90% as a displayed value. However the alarm settings will be at the more usual 85% and 95%. Thus it will be important to determine if the use of these altered POs results in an actual separation of true SpO2 values. This calculation will be performed by back converting the displayed SpO2 values using the actual table of altered values for the high and low oximeters.

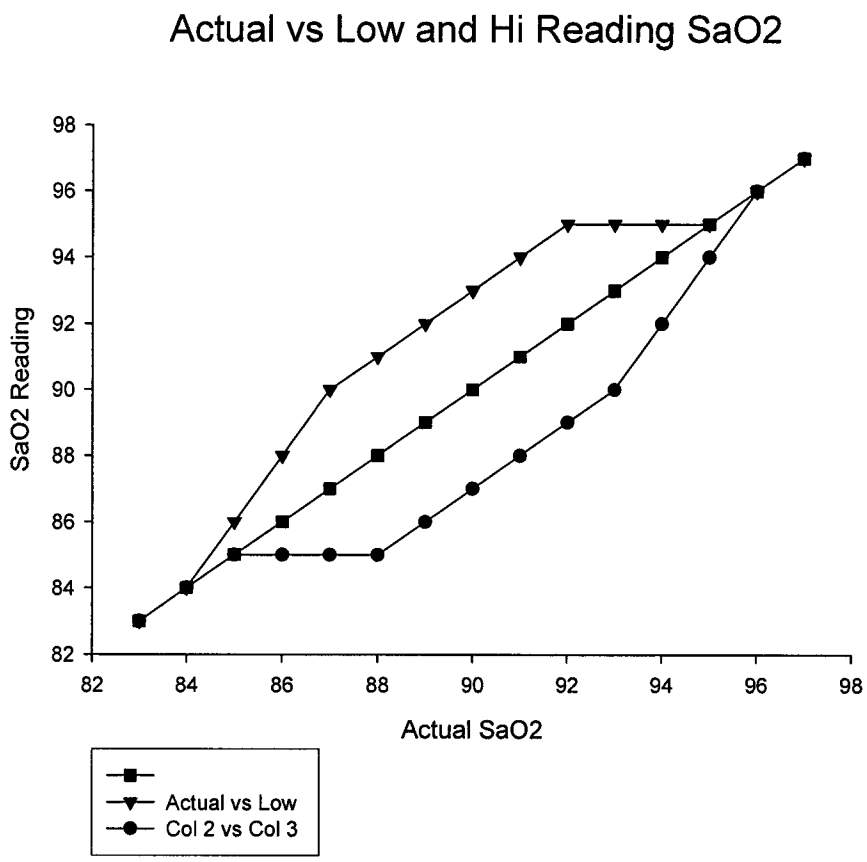
Methods/procedures

Description of the study:

This will be a randomized study, stratified by gestational age and masked to clinicians and investigators. Infants will be randomized during the first week after birth to a low $SaPO_2$ target (85-89%) versus a high $SaPO_2$ (91-95%). The different targeting will be achieved with pulse oximeters that have been electronically altered to provide a varied target output as described below. The pulse oximeters will have unique identifying labels. The oximeters specified in the randomization will be identified by a unique number which will match the number of the pulse oximeter assigned to that infant. An identification code will be maintained by the PI/site coordinator should identification be required for patient safety. RTI will work with Massimo to insure that the POs are labeled with unique identifiers whose code will identify the actual range

of the individual pulse oximeter. An informed consent will be obtained from the parents any time during the first week after birth.

These POs will have an averaging time of 12 seconds and an alarm delay of 12 seconds with a second level alarm for SpO2's < 80%. The target range will be 88-92% and the alarm limits will be 85% to 95% as noted above. This the actual alarms will be activated when the averaged SpO2 is 84% or 96%, and these values are actual, not altered as noted in the above diagram.


Actual vs Low and Hi Reading SaO2
SaO2 Reading
98
96
94
92
90
88
86
84
82
82
84
86
88
90
92
94
96
98
Actual SaO2
Actual vs Low
Col 2 vs Col 3

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO2 range group	88-92%	85-89%	85-95%	85-94%
High SpO2 range group	88-92%	91-95%	85-95%	86-95 %

This system will allow maintenance of masking while at the same time providing a safe margin for alarms to function at the currently used levels.

Randomization will be stratified according to gestational age from 24 07 to 25 6/7 and 26 0/7 to 27 and 6/7 weeks of gestation.

Study population:

Study intervention:

The intervention will be keeping saturations in the low or high targets as described below. All clinical and research personnel will be kept masked to the specific alteration to the monitor used although they will all be aware that an altered output saturation is being used on the patients.

Analysis plan/Sample size estimate:

The primary analysis will be analysis of the continuous outcome of oxygenation index. Infants weaned off the ventilator and CPAP will be considered to have a mean airway pressure of zero, and thus, an oxygen index of zero.

The sample size estimate will be determined in consultation with RTI. The hypothesized effect size is 24% reduction in the oxygenation index. Alternatively, sample size estimate could be based on the median of SPO2 of the two groups of at least four, using a dichotomous analysis. (I would prefer this-Neil)

Available population:

The available population will be over 100 patients per month and completion of the study should be between one and three months depending upon the number of centers doing the pilot study.

---

i Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

ii Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

iii Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

iv Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

v Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

vi Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

vii Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

viii Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

ix Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

x Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

xi Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

xii Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

xiii Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

---

xiv Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

xv Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

xvi Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT TRIAL
Date: Friday, May 07, 2004 1:21:37 PM

Rose, after talking to Ken, we think it would have to be sometime in September.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 07, 2004 1:08 PM
To: 'Hastings, Betty J.'
Subject: RE: SUPPORT TRIAL

On the call today, they wanted to get down to a specific week or two for potential planning.
Thanks
Rose

-----Original Message-----
From: Hastings, Betty J. [mailto:bkh@rti.org]
Sent: Friday, May 07, 2004 1:06 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT TRIAL

Rose,
I'll only be able to seriously start on the forms on the 17th. I have drafted some but it will be quite a while. I would think at least a couple of months (probably longer) because they would have to be reviewed, etc. Ken will need to look into the randomization scheme and if envelopes are to be used, those would have to be prepared as well. It seems that it would be late summer. What do you think?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 07, 2004 12:58 PM
To: 'bkh@rti.org'
Subject: SUPPORT TRIAL

Betty
Neil Finer would like to know a target date for the Support trial training.

Can you help me out??
Thanks
Rose
Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: ProFox Software
Date: Wednesday, May 12, 2004 9:44:39 AM

Cost is in addition of oximeters.
One per site.
Software is from a stand-alone company, and they actually wrote a version
specifically for us and STOP-ROP. I did not know they would charge us, but the time
savings and improved odds of getting data from all sights seem worth the investment to me.

wade

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 12, 2004 3:13 AM
To: 'wrich@ucsd.edu'
Subject: Re: ProFox Software

Was this price already in the 2000 dollar oximeter cost or in addition?is one needed per hospital site? Thanks Rose
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wade Rich <wrich@ucsd.edu>
To: 'Neil Finer' <nfiner@ucsd.edu>
CC: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue May 11 14:36:54 2004
Subject: ProFox Software

Neil, Rose,

ProFox, the oximetry acquisition software we would like to use for SUPPORT (and the one being used by STOP-ROP) is going to cost us $250.00 per site. It has been modified to allow only the entry of a patient number instead of a name, the data can not be changed, and is sent immediately to an ASCII file without any intervention by the downloader. I think we should purchase the software for the 5 centers involved in the pilot study first, in case either the software or oximeters have a glitch.
This being said, it occurs to me that we will need a way to download the oximters in the unit. I suspect many programs have a laptop they can use for this project, but if not they will need to purchase one. If the network ends up supplying/purchasing them, I am willing to have them all sent here for installation of software and testing before sending them out to sites.

Wade

Wade Rich, RRT-NPS
Clinical Research Administrator
Division of Neonatology

UCSD Medical Center
200 W Arbor Dr
San Diego, CA 92103-8774
619-543-5375
pgr 290-5230

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT reviews
Date: Friday, May 14, 2004 4:36:13 PM

Hi Rose-

Bethany was wondering were we are in the SUPPORT trial outside review process. I thought we sent the trial out for review and Neil has addressed all of their concerns.

Please advise.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Edward Donovan
To:	Edward Donovan; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc:	bkh@rti.org
Subject:	SUPPORT training
Date:	Monday, May 17, 2004 4:41:12 PM
Attachments:	Survey of Network center CPAP use in preparation for SUPPORT training.doc

In preparation for the support training session, I would like to send out a questionnaire regarding CPAP practices in Network centers.

Please review the attached questionnaire and send me comments and suggestions.

Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

Center _____

Survey of Network center CPAP use in preparation for SUPPORT training

1. For VLBW infants in your center receiving CPAP, what proportion receive ET vs nasal CPAP?

   ET CPAP ___%
   Nasal CPAP ___%

2. Do some VLBW infants in your center receive nasal CPAP?

   Yes ___ No ___

   More than 5 infants per month? __
   More than 10 infants per month? __

3. Do some ELBW infants in your center receive nasal CPAP?

   Yes ___ No ___

   More than 5 infants per month? __
   More than 10 infants per month? __

3. What nasal apparatus is most often used for VLBW nasal CPAP in your center?

   Short nasal prongs ___ Brand _____
   Long nasal prongs ___ Brand _____
   Nasal mask ___ Brand _____
   Other ___ Brand _____

4. For VLBW infants receiving CPAP, does CPAP typically begin in the delivery room?

   Yes ___ No ___

5. Please rank, from most to least common, the indications for CPAP in your nursery:

   Management of RDS ___
   Management of apnea ___
   Management of the post-extubation period ___
   Other, explain _____ ___

6. What device is most commonly used for delivering CPAP pressure in your center (choose one)?

   "Home made" underwater seal ___
   Other underwater seal ___
   Commercial CPAP device ___
   List brand and model_____
   Ventilator ___
   List brand and model_____

7. Is CPAP commonly used for more than 3 days in an individual VLBW infant?

   Yes ___ No ___ _____

8. Are VLBW infants in your center fed while receiving CPAP in your center?

   Yes ___ No ___ _____

9. Does your center routinely use an indwelling nasogastric tube in infants receiving nasal CPAP?

   Yes ___ No ___ _____

From:	Higgins, Rosemary (NIH/NICHD)
To:	"bkh@rti.org"; "poo@rti.org"
Subject:	FW: SUPPORT training
Date:	Monday, May 17, 2004 4:44:46 PM
Attachments:	Survey of Network center CPAP use in preparation for SUPPORT training.doc

Betty and Ken
This looks OK by me
Rose
-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Monday, May 17, 2004 4:41 PM
To: Edward Donovan; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc: bkh@rti.org
Subject: SUPPORT training

In preparation for the support training session, I would like to send out a questionnaire regarding CPAP practices in Network centers.

Please review the attached questionnaire and send me comments and suggestions.

Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Avroy A. Fanaroff
To: Edward.Donovan@cchmc.org; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; nfiner@ucsd.edu; Edward.Donovan@cchmc.org
Cc: bkh@rti.org
Subject: Re: SUPPORT training
Date: Monday, May 17, 2004 4:50:07 PM

Hi
The questionnaire looks fine
I am not a big fan of questionnaires - do you intend to standardize treatment?
What do you hope to gain from this information?
Regards
Av

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

From: Edward Donovan
Date: 05/17/04 16:41:21
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc: bkh@rti.org
Subject: SUPPORT training

In preparation for the support training session, I would like to send out a questionnaire regarding CPAP practices in Network centers.

Please review the attached questionnaire and send me comments and suggestions.

Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

From: Higgins, Rosemary (NIH/NICHD)
To: Berberich, Mary Ann (NIH/NHLBI)
Subject: SUPPORT TRIAL
Date: Tuesday, May 18, 2004 8:08:14 AM
Attachments: SUPPORT Trial graph Final 04_05.doc
SUPPORT Trial March 23 final.doc

Mary Ann
In preparation for our meeting on Thursday, I am attaching the latest version of the SUPPORT TRIAL protocol. I have also attached a table which the investigators have generated outlining the critical points for the study. I spoke to Ken Poole, our data center PI. He can arrange the collection so that early in the study, pairs of study subjects can be evaluated to insure safety. Following an initial evaluation (we tell him how many patients), an analysis for safety outcomes can be done every 30 or so patients. Think about this and we can discuss this at the meeting Thursday. I will have my blackberry on today and tomorrow if you have other 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 Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From:	Wally Carlo, M.D.
To:	nfiner@ucsd.edu; Wade Rich
Cc:	Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD)
Subject:	Oxygenation Trial
Date:	Tuesday, May 18, 2004 5:44:59 PM
Attachments:	PILOT STUDY OXYGENATION TRIAL IN ELBW INFANTS revised 5 18 04 NF-2.doc

Dear Neil and Wade: Enclosed is the revised protocol on the pilot study for the oxygenation trial. I have made the suggested changes. I left the protocol for the first week after birth as it will be quite easy to enroll a sufficient number of babies. This will also be an easier transition as we start enrolling patients into the main trial. I think we are ready to go. I will start working on the data collection forms. Thanks for your help. I did not get comments from other members of the Committee. You may want to send it again just to make sure that they are ok. I think everyone was ok with it during the conference call so I do not think there should not be major concerns now.

Best regards, Wally

P.S. I had to make some changes on the numbers of the table as they were incorrect. Please verify them.

Pilot Study for the Oxygenation Trial in Extremely Low Birth Weight Infants

Abstract

Objective: To determine if infants managed with a higher SpO_2 target (91-95%) for 24 hours during the first week after birth will result in at least a 3% lower SpO_2 than infants managed with a lower saturation target (85-89%).

Study Design: Multicenter, randomized masked trial.

Eligibility Criteria: Subjects will be infants of 24 0/7 to 27 6/7 weeks who are receiving mechanical ventilation on continuous positive pressure during the first week after birth.

Study Intervention: Infants will be randomized to high or low saturation targets and FiO_2 and ventilator settings will be adjusted by clinicians to accomplish the clinically desired saturation targets. Alarm limits will be set at 85 and 95 %. Clinical targets will be within this range. Infants in both groups will be monitored for adverse events including desaturations below 80% and below 85% and for metabolic acidosis (bicarbonate level).

Primary Outcome Measure: Separation of median SpO_2 by at least 3%.

Sample Size Estimate: The number of infants to be enrolled will be determined with RTI's advice.

Statement of problem

Oxygen saturation (SpO_2) targets in infants vary markedly between centers and there is no consensus on the targets that optimize outcomes. Published acceptable levels of SpO_2 in neonates range from 85 to 98%. Even lower SpO_2 targets have been used in neonates with apparent safety. Keeping SpO_2 targets in the high side of this range may have short term benefits such as prevention of desaturation, vasoconstriction and bronchoconstriction episodes. In addition, in infants with prethreshold retinopathy of prematurity (ROP), progression to threshold ROP may be reduced with higher SpO_2 targets even though ROP increased incidence may be when high SpO_2 targets are used. However, a randomized controlled trial of infants beyond the first month after birth reported that SpO_2 in the high 90s did not improve long term outcomes but worsened pulmonary outcomes. In contrast, there has been concern that keeping low SpO_2 values may result in cerebral palsy and that higher SpO_2 values may prevent neurodevelopmental impairment. A consensus conference on assisted ventilation concluded that blood gas targets do not have to be in the "normal" ranges and that lower than normal SpO_2 targets may be preferable for ventilated patients. However, there is no consensus of optimal SpO_2 targets in neonates. Targeting lower SpO_2 than commonly used currently (90s) may lead to a lower incidence of bronchopulmonary dysplasia and retinopathy of prematurity.

A recent randomized controlled trial targeted SpO_2 between 91 to 94% versus 95 to 98% in preterm infants born at less than 30 weeks of gestational age when they had reached a postmenstrual age of 32 weeks. This large randomized controlled trial reported that there was no

improved growth or neurodevelopment (blindness, cerebral palsy or developmental quotient) by keeping SpO_2 95 to 98%. However, targeting high SpO_2 resulted in a longer period of oxygen supplementation after randomization (40 versus 18 days) and a higher dependence on oxygen supplementation at 36 weeks and after discharge. A study to target high SpO_2 in infants with prethreshold ROP showed that there was a decreased progression to threshold ROP but there was a prolongation of oxygen supplementation and hospitalization with a target of higher SpO_2.

However, these studies have targeted SpO_2 in infants beyond the first month after birth. It is necessary to determine the desired oxygen targets in infants starting in the first days after birth because lung injury, ROP, and other complications due to high or low SpO_2 may start early after birth or take a longer time to develop.

The current pilot study will be a short term study to test the feasibility of aiming for two different targets of SpO_2, one of which is around the lower limit of current practice in many centers (85-89%) and the other on the upper limit (91-95%).

Hypothesis

We hypothesize that relative to infants managed with a higher SpO_2 target (91-95%) for 24 hours during the first week after birth, that the use of a lower SpO_2 (85-89%) will result in lower median saturation by at least 3%.

We hypothesize that relative to infants managed with higher target range (91-95%), the use of a lower SpO_2 (85 to 89%) for 24 hours during the first week after birth will result in:

Secondary hypotheses:

1) an improvement in oxygenation index for infants on a ventilator.

2) no change in $PaCO_2$, bicarbonate, or pH.

3) desaturation below 80% and below 75%

4) no unblinding of the caretakers

Study subjects will be infants of 24 and 0/7 to 27 and 6/7 weeks if they are receiving mechanical ventilation or continuous positive airway pressure. Infants will be stratified into two gestational age strata from 24 0/7 to 25 6/7 weeks and from 26 0/7 to 27 6/7 weeks, obtained by best estimate of gestational age according to the GDB stipulated hierarchy.

Inclusion criteria are as follows:

1) 24 0/7 week to 27 6/7 week

2) Infants receiving CPAP or mechanical ventilation with a > 30% oxygen supplementation.

Exclusion criteria are as follows:

1) Infants outside of the gestational age window at birth or beyond the first week after birth

2) Infants whose parents/legal guardians refuse consent

3) Infants born during the time when the research study personnel are not available.

Rationale/justification

It is still unknown what the optimal $SaPO_2$ targets are for infants during the first week after birth and whether targeting different saturations actually result in distinct ranges of saturations in infants. The approved Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) of the NICHD Neonatal Research Network will test whether targeting oxygen saturations for a prolonged period results in improvement in important clinical outcomes. The purpose of this pilot study is to determine if during a 24 hour period, targeting different saturation ranges results in different SpO_2 levels in these infants.

Background/previous studies

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality (1).

Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD (2,3,4). For example, the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants (5). Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease (6).

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported that infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen (7, 8). Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life (9). A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal mortality in infants resuscitated with room air (6 vs 11%, $p<0.005$, OR 0.57, 95% CI 0.40 – 0.81) (10). While these studies described results of mostly

term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al. resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher median (interquartile range) cerebral blood flow compared with oxygen resuscitated infants: 15.9 (13.6-21.9) vs 12.2 (10.7-13.8) ml/100 g/minute) (11). They did not find any significant differences in short or long-term outcomes but did note that SpO_2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO_2 may increase to very high levels, as there are rapid increases in PaO_2 with very small increments in SpO_2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO_2 ranges (88%-98%) (12). They reported that infants who were managed for at least the first 8 weeks of life with SpO_2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO_2 ranges. Infants managed with the lower SpO_2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al. using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to

infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants ≥ 1100gm, there was a decrease in the incidence of ROP (13). The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO_2 less than 94% to two ranges of SpO_2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO_2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD (14).

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO_2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization (15). The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO_2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO_2 ranges that were actually achieved in their infants, and thus it is uncertain

whether their observed reductions in ROP were related to the altered SpO_2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO_2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted compared SpO_2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; $P<0.001$) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy but resulted in an increased duration of oxygen supplementation (16). They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months.

There is a need to determine that the use of altered pulse oximeters lead to a difference of actual saturations between the groups but will not lead to inadvertent unblinding of the primary care taker. There is a need to also determine that the use of common alarm limits will not interfere with achievement of the separation of SpO_2 values. The entire range of displayed SpO_2 values is altered either high or low from 85% to 95%. The maximum difference between the high and low

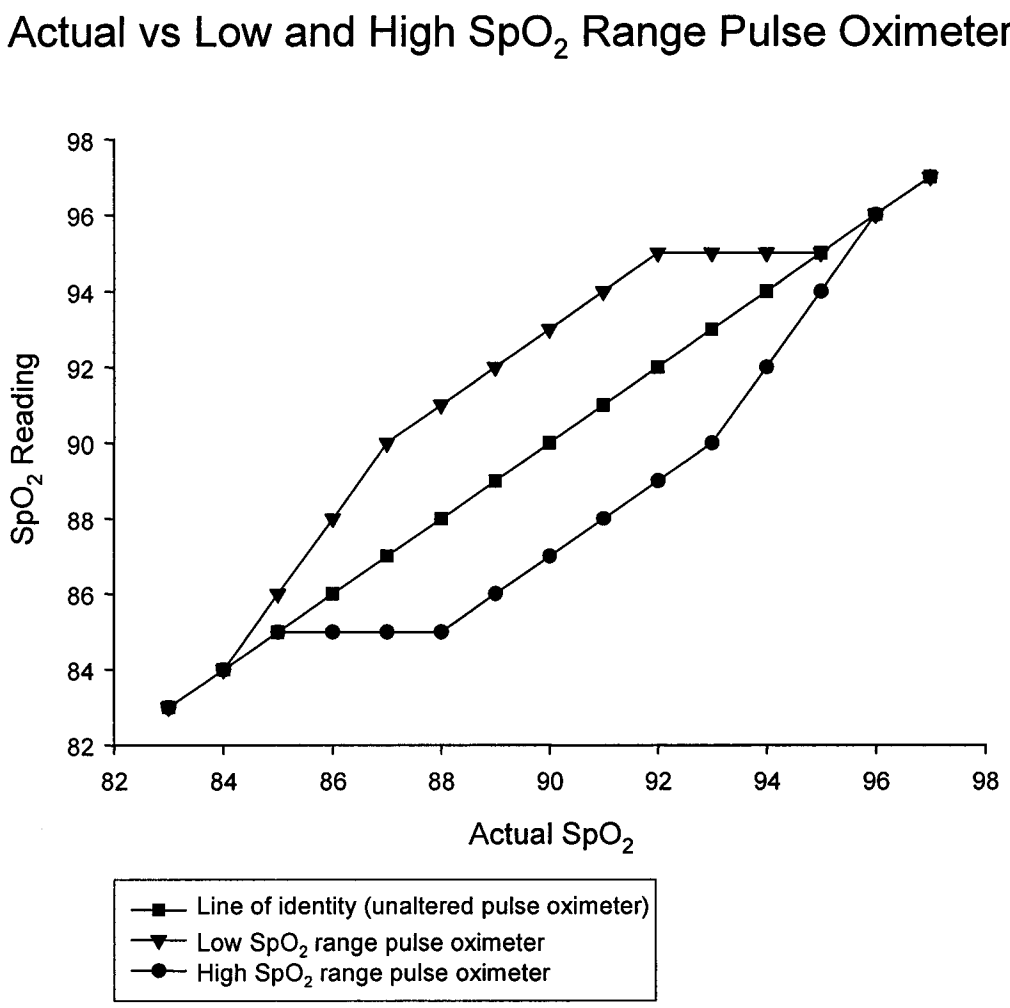
pulse oximeters will be at the center of the target range, approximately 90% as a displayed value. However, the alarm settings will be at the more usual 85% and 95%. Thus it will be important to determine if the use of these altered pulse oximeters results in an actual separation of true SpO_2 values. This calculation will be performed by back converting the displayed SpO_2 values using the actual table of altered values for the high and low oximeters.

Methods/procedures

Description of the study:

This will be a randomized pilot study, stratified by gestational age and masked to clinicians and investigators. Infants will be randomized during the first week after birth to a low SpO_2 target (85-89%) versus a high SpO_2 (91-95%). The different targeting will be achieved with pulse oximeters that have been electronically altered to provide a varied target output as described below. The pulse oximeters will have unique identifying labels. The oximeters specified in the randomization will be identified by a unique number which will match the number of the pulse oximeter assigned to that infant. An identification code will be maintained by the PI/site coordinator should identification be required for patient safety. RTI will work with Massimo to insure that the pulse oximeters are labeled with unique identifiers whose code will identify the actual range of the individual pulse oximeter. An informed consent will be obtained from the parents.

The pulse oximeters will have an averaging time of 12 seconds and an alarm delay of 12 seconds with a second level alarm for SpO_2's < 80%. The target range will be 88-92% and the alarm limits will be 85% to 95% as noted above. This the actual alarms will be activated when the averaged SpO_2 is 84% or 96%, and these values are actual, not altered as noted in the above diagram.



Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO_2 range group	88-92%	86-89%	85-95%	84-96%
High SpO_2 range group	88-92%	91-94%	85-95%	84-96%

This system will allow maintenance of masking while at the same time provide a safe margin for alarms to function at the currently used levels.

Randomization will be stratified according to gestational age from 24 0/7 to 25 6/7 and 26 0/7 to 27 6/7 weeks of gestation.

Study population:

The study population will be obtained by convenience sampling of eligible infants who meet inclusion/exclusion criteria.

Study intervention:

The intervention will be keeping saturations in the low or high targets as described below. All clinical and research personnel will be kept masked to the specific alteration to the monitor used although they will all be aware that an altered output saturation is being used on the patients.

Analysis plan/Sample size estimate:

The primary analysis will be analysis of the continuous outcome of oxygenation index. Infants weaned off the ventilator and CPAP will be considered to have a mean airway pressure of zero, and thus, an oxygen index of zero.

The sample size estimate will be determined in consultation with RTI. The sample size estimate will be based on the median of SpO_2 of the two groups of at least three, using a dichotomous analysis.

Available population:

The available population will be over 100 patients per month and completion of the study should be between one and three months depending upon the number of centers doing the pilot study.

References:

1. Silvers KM, Gibson AT, Russell JM, Powers HJ. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Arch Dis Child 78:F214-F219, 1998.
2. Saugstad OD. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Pediatr 86:1277-1282, 1997.
3. Luo XP, Jankov RP, Ning Q, Liao LJ, Tanswell AK. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacol Sinica 2322-2328, 2002.
4. Davis JM. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Pediatr 9123-9125, 2002.
5. Rozycki HJ, Comber PG, Huff TE. Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. Am J Physiol Lung Cell Mol Physiol 282:L1222-L1228, 2002.
6. Varsila E, Pesonen E, Andersson S. Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Pediatr 84:1296-1299, 1995.
7. Ramji S, Ahuja S, Thirupuram S, rootwelt T, Rooth G, Saugstad OD. Resuscitation of asphyxic newborn infants with room air or 100% oxygen. Pediatr Res 34:809-812, 1993.
8. Saugstad OD, Rootwelt T, Aalen O. Resuscitation of asphyxiated newborn infants with room air or oxygen: an international controlled trial: The Resair 2 study. Pediatrics 102:E11-E17, 1998.
9. Vento M, Asensi M, Sastre J, GarciaSala F, Pallardo FV, Vina J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics 107:642-647, 2001.

10. Saugstad OD, Ramji S, Vento M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003.

11. Lundstrom KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Arch Dis Child 73:F81-F86, 1995.

12. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal neonatal 84:F106-F110, 1995.

13. Bancalari E, Flynn J, Boldberg RN, Bawol R, Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics 79:663-669, 1987.

14. Phelps DL, Lindblad A, Bradford JD, Wood NE, Oden NL, Cole C, et al. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial I: Primary outcomes. Pediatrics 105:295-310, 2000.

15. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 111:339-345, 2003.

16. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 349:953-961, 2003.

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Cc: Neil Finer
Subject: RE: O2 pilot
Date: Wednesday, May 19, 2004 1:27:28 PM

Rose: I think it will be about 100 or so. We plan to use it as a roll in into the main trial. The idea is that we would not delay the enrollment of the main trial. Indeed, we would continue to collect the pilot data after we start enrollment in the main trial until we reach the sample size. Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, May 19, 2004 12:10 PM
To: Wally Carlo, M.D.
Subject: Re: O2 pilot

Wally
I read the protocol - do you have any guess on sample size??

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Wed May 19 08:19:33 2004
Subject: O2 pilot

Rose: I sent you a copy of the protocol yesterday. Please let me know if we can proceed with IRB submission. Thanks, wally

---

From: Edward Donovan
To: James Greenberg
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Dates for SUPPORT Training
Date: Thursday, May 20, 2004 11:55:17 AM

Haven't heard yet.
Will let you know.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> Jim Greenberg <james.greenberg@cchmc.org> 05/20/2004 9:24:44 AM >>>
Hi Ed-

Are the dates confirmed for the SUPPORT Trial meeting? Looking at the calendar, I find that Wednesday evening, September 15 is the first night of Rosh Hashanah. For what it's worth, I'd prefer to do it the week before (September 7, 8, 9).

Let me know when you have the dates confirmed.

Thanks,

Jim

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD); petrie@rti.org
Subject: Fwd: SUPPORT Trial Kingsgate Room Availability
Date: Wednesday, May 26, 2004 2:52:54 PM
Attachments: SUPPORT Trial Kingsgate Room Availability.msg

---

fyi

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

Blansfield, Earl (NIH/NICHD) [E]

From: Janel Chriss <Janel.Chriss@cchmc.org>
Sent: Wednesday, May 26, 2004 12:40 PM
To: Diane Timmer; Estelle Fischer; Barb Alexander
Cc: Edward Donovan; Judy Kellogg
Subject: SUPPORT Trial Kingsgate Room Availability

All,

FYI.....

I just spoke with Rhonda Freeman at Kingsgate, she told me the week of Sept 7 would not be a good week as for room availability or a large conference room to house the luncheon. Currently the best week would be the week of Sept. 13 as rooms are available and they may have a conference room available on the 15th (currently there is something tentativly booked for that date she will get back to me tomorrow).

I want to make sure that I am clear as to the amount of rooms; Group A (32 people) would come in on Monday night and leave either Wednesday night or Thursday morning, Group B (32 people) would come in on Tuesday night and leave either Thursday evening or Friday morning. If this is correct then we will need 32 rooms for Monday thru Thursday and an additional 32 rooms for Tuesday thru Friday. Please let me know if this is incorrect. As I said they have rooms available today for the week of Sept 13, but if we wait till next week to book them we may very well loose them.

If you have any questions, please give me a call.

Thanks

Janel Chriss
Services Coordinator II
Division of Neonatology
Cincinnati Children's Medical Center
513-636-5470 - phone
513-636-4404 - fax

From: Poole, W. Kenneth
To: "Susan Hintz"
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: FW: need some numbers
Date: Thursday, May 27, 2004 4:41:50 PM
Attachments: born 2003.doc

Your request.

1 -- 1468 were enrolled
2 -- 1249 survived > 7 days
3 -- 1209 survived >= 14 days
4 -- 1027 were discharged home
5 -- 243 (20.3%) with grade 3/4 IVH of those who survived >= 14 days
6 -- 189 (18.6%) with grade 3/4 IVH of those who survived to discharge
7 -- 40 (3.9%) with PVL of those who survived to discharge (based on 1023)

The attached Word document has all the info.

1) Number of infants 24+0 to 27+6 weeks EGA enrolled in GDB (for year 2003)
2) Number of infants 24+0 to 27+6 weeks EGA enrolled in GDB surviving > 7 days (for year 2003)
3) Number of infants 24+0 to 27+6 weeks EGA enrolled in GDB surviving >=14 days (for year 2003)
4) Number of infants 24+0 to 27+6 weeks EGA surviving to hospital discharge (for year 2003)
5) Number and proportion of infants 24+0 to 27+6 weeks EGA surviving >=14 days with Grade III or IV IVH on head US (for year 2003)
6) Number and proportion of infants 24+0 to 27+6 weeks EGA surviving to hospital discharge with Grade III or IV IVH on head US (for year 2003)
7) Number and proportion of infants 24+0 to 27+6 weeks EGA surviving to hospital discharge with PVL (year 2003). For this question I definitely need to know the number of infants for whom data was ENTERED.

The FREQ Procedure

Gestational Age at Birth

gest_age	Frequency	Percent	Cumulative Frequency	Cumulative Percent
24	314	21.39	314	21.39
25	349	23.77	663	45.16
26	383	26.09	1046	71.25
27	422	28.75	1468	100.00

Status of Infant at Time of Completetion

OCGSTAT	Frequency	Percent
Discharged to home	751	52.96
Still in hospital at 120 days	206	14.53
Transferred to another hospital	115	8.11
Transferred to chronic care facility	1	0.07
Death	345	24.33

Status of Infant at Time of Completetion

OCGSTAT	Cumulative Frequency	Cumulative Percent
Discharged to home	751	52.96
Still in hospital at 120 days	957	67.49
Transferred to another hospital	1072	75.60
Transferred to chronic care facility	1073	75.67
Death	1418	100.00

Frequency Missing = 50

Final Status

finlstat	Frequency	Percent
Discharged to home	1027	72.32
Still in hospital at 120 days	20	1.41
Transferred to another hospital	9	0.63
Death	361	25.42
Remains in hospital at one year	3	0.21

The FREQ Procedure

Final Status

finlstat	Cumulative Frequency	Cumulative Percent
Discharged to home	1027	72.32
Still in hospital at 120 days	1047	73.73
Transferred to another hospital	1056	74.37
Death	1417	99.79
Remains in hospital at one year	1420	100.00

Frequency Missing = 48

Survived > 7 Days

surv8	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	1249	87.90	1249	87.90
No	172	12.10	1421	100.00

Frequency Missing = 47

Survived >= 14 Days

surv14	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	1209	85.20	1209	85.20
No	210	14.80	1419	100.00

Frequency Missing = 49

The FREQ Procedure

ivhgr34	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	243	20.27	243	20.27
No	956	79.73	1199	100.00

Frequency Missing = 10

The FREQ Procedure

ivhgr34	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	189	18.55	189	18.55
No	830	81.45	1019	100.00

Frequency Missing = 8

pvl	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Yes	40	3.91	40	3.91
No	983	96.09	1023	100.00

Frequency Missing = 4

From: Edward Donovan
To: WCarlo@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT training
Date: Saturday, May 29, 2004 1:36:55 PM

Rose sent out a couple of choices to all centers. I haven't heard back yet. I'm hoping that the choice is second week in Sept.
Will let you know.
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu
>>> "Wally Carlo, M.D." <WCarlo@peds.uab.edu> 05/28/04 11:56 PM >>>
Ed: Have you made a decision about the dates of training? Wally

---

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Monday, May 17, 2004 3:41 PM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc: bkh@rti.org
Subject: SUPPORT training

In preparation for the support training session, I would like to send out a questionnaire regarding CPAP practices in Network centers.

Please review the attached questionnaire and send me comments and suggestions.

Thanks,
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
HYPERLINK "http://www.cprc-chmc.uc.edu"www.cprc-chmc.uc.edu

From: Edward Donovan
To: Diane Timmer
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: SUPPORT Trial
Date: Saturday, May 29, 2004 7:48:55 PM

I would put room on hold.
I'll check on whether we need breakout rooms on Weds.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu
>>> Diane Timmer 05/27/04 3:12 PM >>>
Janel Chris and I are doing some preliminary work on various aspects of setting up this meeting. We realize a lot of this will probably be hashed out in the meeting Tuesday. She has been in touch with Kingsgate to feel them out for availability in September.

Kingsgate has a room which will accommodate 80 people in rounds (not their ballroom) on the 15th, plus we could block sleeping rooms -- but not for the week before.

We have plans to check the room out next week. The question is -- is everything going to be self-contained in the one big room on Wednesday (she said something about the speaker being during lunch), will there be breakout rooms needed?

She is a bit jittery about this room being taken. I suggested she try to get a temporary hold on this until we meet on Tuesday. Any input at this point?

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD)
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: delivery room CPAP/ oxygen saturation trial
Date:	Monday, March 01, 2004 3:46:13 PM

Thanks Rose
The Ventilator committee requested that we have an interested PI from each site take on this role. Can I now discuss with Masimo??
Be well
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (E-mail) ; Carlo Waldemar (E-mail) ; Charles Rosenfeld ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Fanaroff Avroy (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; Michelle Walsh ; Neil Finer ; Oh William (E-mail) ; Poole Kenneth (E-mail) ; Ronald GOldberg ; Shahnaz Duara ; Shankaran Seetha (E-mail) ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; Walid Salhab (E-mail)
Cc: 'petrie@rti.org' ; 'bkh@rti.org'
Sent: Friday, February 27, 2004 12:24 PM
Subject: delivery room CPAP/ oxygen saturation trial

Hi,
I have received a few requests to have "site PI's" for the upcoming DR CPAP trial. I believe this is an excellent idea and if PI's would like another neonatologist at their site to be the PI for this project let me know.

In addition, it is highly likely that we will receive co-funding for this project from National Heart Lung and Blood Institute for which I am extremely grateful.

Have a good weekend!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Neil Finer
To: Ed Donovan; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.
Subject: COT ?Final Protocol
Date: Thursday, March 11, 2004 9:30:10 PM
Attachments: COT Trial March 11 04.doc
COT Schema.ppt

Hello Everyone
I am trying to keep my promise that this protocol will be good to go before mid-March
I am attaching the most current Mar 11 Version. Please give it a final look. I have made a few more changes based on some critiques that I have received.
I have copied below the new or changed areas.
I have called the groups CPAP and Early surfactant

: **Surfactant**

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant

***Extubation*:**

Extubation ***MUST*** be attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks.
Extubation without meeting these criteria will be considering a protocol violation.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

Note that I have used an SpO2 of 88% as the criteria as this is the low end of the target range and is more consistent with our use of these ranges.

Wide Target ± 1 Alarm	**CRT Output Target**	**Actual Target**	**CRT Output Alarm Limits Will alarm above or below these values**	**Actual Alarm Values**
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

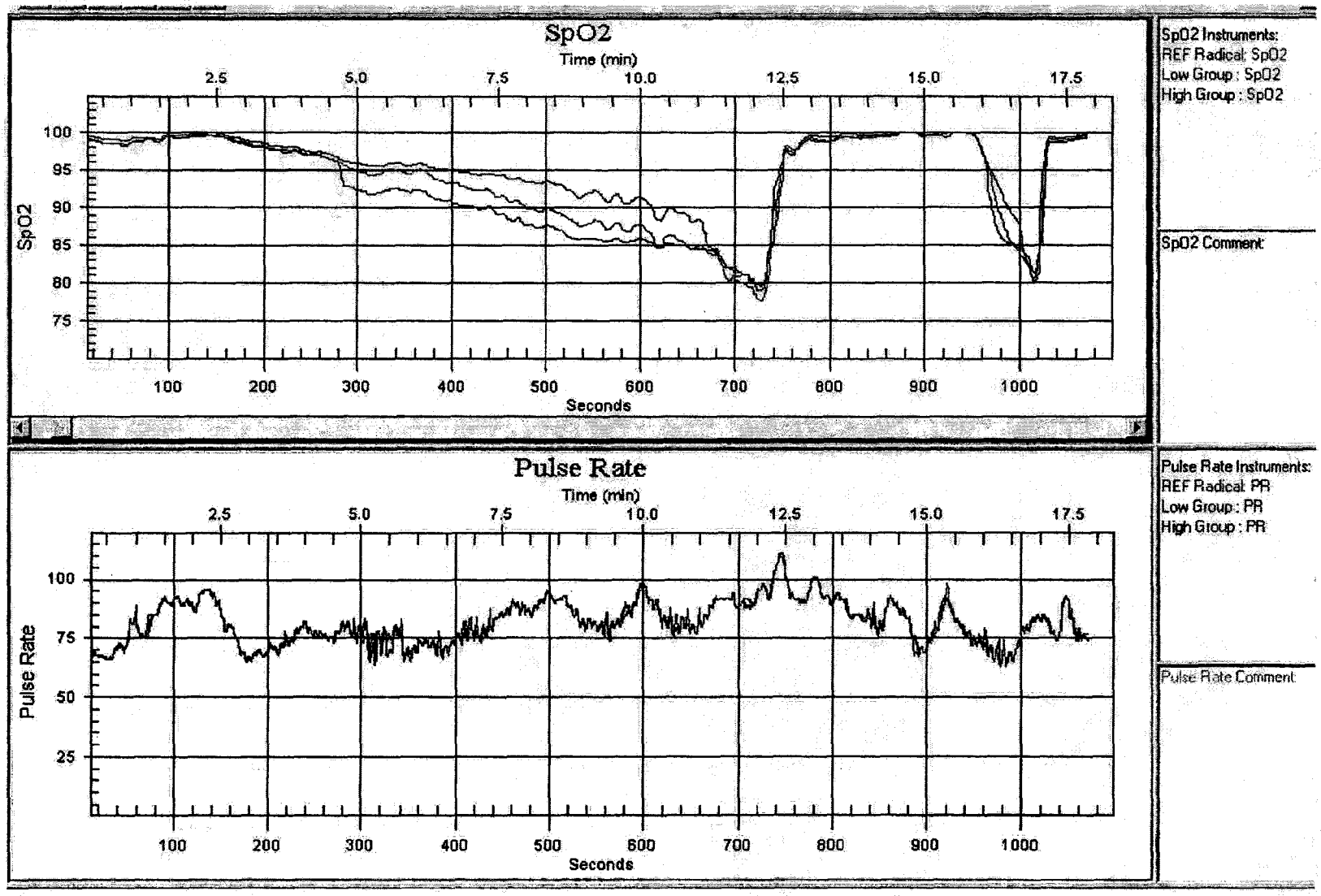
This is a correction as the alarms will actually sound at 84% and 96%

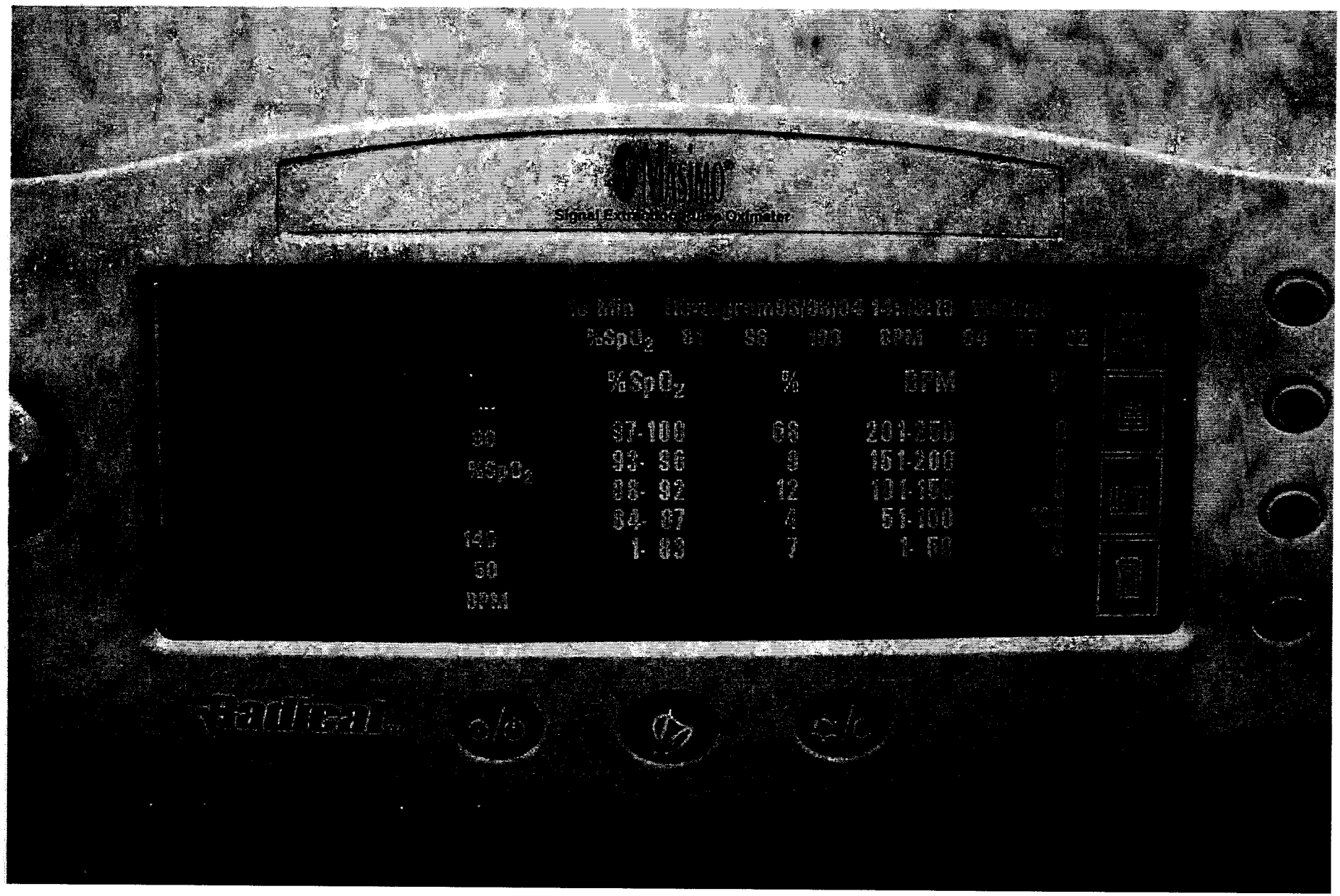
Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values

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. Our

analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

In addition I have attached the actual pulse oximeter outputs as tested by Masimo. These look OK to us. Your thoughts??
I will be in Australia next week, so I will check back with you in a week. Please let Rose know if we can proceed with this version. In addition, I would like to have Wally's pilot for the POs approved so that the 5 sites can begin. I have asked Masimo for 20-25 test devices.
Be well
Neil


SpO2
Time (min)
2.5
5.0
7.5
10.0
12.5
15.0
17.5
100
95
90
85
80
75
SpO2
100
200
300
400
500
600
700
800
900
1000
Seconds
SpO2 Instruments:
REF Radical: SpO2
Low Group : SpO2
High Group : SpO2
SpO2 Comment
Pulse Rate
Time (min)
2.5
5.0
7.5
10.0
12.5
15.0
17.5
100
75
50
25
Pulse Rate
100
200
300
400
500
600
700
800
900
1000
Seconds
Pulse Rate Instruments:
REF Radical: PR
Low Group : PR
High Group : PR
Pulse Rate Comment


Masimo
Signal Extraction Pulse Oximeter
%SpO2
BPM
Radical

Protocol for the NICHD Neonatal Research Network

Continous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

Mar 11, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

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. 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 COT 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 ≥ 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.

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.[51] 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[52] using a 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.[53] 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 (≤ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 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.[54] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for te 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 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 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 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 $\geq$ 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

Neopuff resuscitators, equivalent T-piece resuscitators or a Neonatal ventilator including disposable circuits, will be provided to all sites for delivery room management. Sites may use equivalent devices that are already available. A training video to explain the proper use of the Neopuff® will be provided to each site in advance of a site visit. If available CPAP will be provided by the Bubbleflow device (Fisher&Paykel, Auckland, NZ). This device is currently under FDA consideration. We may apply for an IDE to use this device for this trial if it has not received FDA approval prior to trial initiation

3.7 Randomization

Gestation-specific, stratified. Randomization 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 are being randomized to different treatment arms.

Each randomization will indicate randomization to either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and to 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 1 hour following NICU admission.

CPAP Group : Early Extubation and CPAP – Both Strata

Delivery Room Management

FiO2:

Infants will be resuscitated using whatever FiO_2 represents current practice in each unit

CPAP:

CPAP or positive pressure ventilation with PEEP utilized if the infant requires positive pressure ventilation, PPV during resuscitation for stabilization. The CPAP is continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. The Neopuff® or equivalent (See Section **3.6**) will be used to deliver initial CPAP in the delivery room.

It is acceptable to insert nasal prongs in the delivery room and transport on such a device with CPAP or PPV/PEEP to the NICU.

Intubation:

Infants who require intubation for resuscitation will receive surfactant in the DR area at the discretion of the attending physician, or once in the NICU, with the recommendation that such surfactant be given within 30 $\pm$30 min minutes of birth for infants who required DR intubation.

Thus earlier 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. This was the approach used for the DR CPAP feasibility trial.

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice, apart from the restriction that treatment infants may not be intubated for sole purpose of giving surfactant in the delivery room (DR).

NICU Management

These infants will be managed on nasal CPAP, and 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:

CPAP-Treatment infants may only be intubated if they meet ANY of these criteria and given surfactant (within the first 48 hours of life in the presence of respiratory distress)

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

(The average duration of ventilation of such infants is 21 days for infants of 24-25 weeks and 6 days for infants of 26-27 weeks for all centers)

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation:

An intubated Treatment infant *MUST have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable

These criteria will continue in effect for 14 days of life for 24-25 weeks and 7 days for 26-27 weeks.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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- Early Surfactant Group: Prophylactic/Early Surfactant and Ventilation

Overview:
Control infants are to be treated using an approach considered similar to current standards of care. The requirements for intubation of such infants are based on the best evidence to date suggesting that prophylactic surfactant by 15 minutes or early surfactant within 2 hours of birth provide a significant survival benefit. This approach will be used for all infants in the all Control Infants in both strata.

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.

Delivery Room Management :
Infants will be intubated in the delivery room and given surfactant or receive surfactant within 30 $\pm$ 30 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:
Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**
Extubation ***MUST*** be attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 $\leq$ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks.
Extubation without meeting these criteria will be considering a protocol violation.

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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study violation.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous..

The protocol will require that all eligible infants in the Control stratum are intubated and receive prophylactic/early surfactant.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 7 days of life for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks.

For all Infants, Both Strata

For any infant in any arm of this trial, 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. All the above criteria will be in effect for the first 14 days of life for the 24 to 25 6/7ths week stratum and 7 days for the 26 to 276/7ths week stratum, following which current unit practice will dictate management.

The protocol requires that surfactant be administered to any infant intubated within 48 hours of birth, who has not previously received surfactant.

Repeat surfactant dosing should follow the manufacturers' recommendations for dose and interval, and criteria are indicated in the protocol. Repeat dosing is not required by the study protocol.

There is no requirement for the use of caffeine and its use should follow center practice. Similarly indomethacin use will follow current center practice.

Nasal SIMV may be used for any infant in the trial *only following extubation*. It may not be used for Treatment infants randomized to receive CPAP, who have not been intubated. In addition the above intubation criteria will apply to all infants irrespective of whether they are receiving Nasal SIMV.

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) 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 94%. 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 gradually 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 following NICU admission, with a maximal allowable delay of 60 minutes. 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% to 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

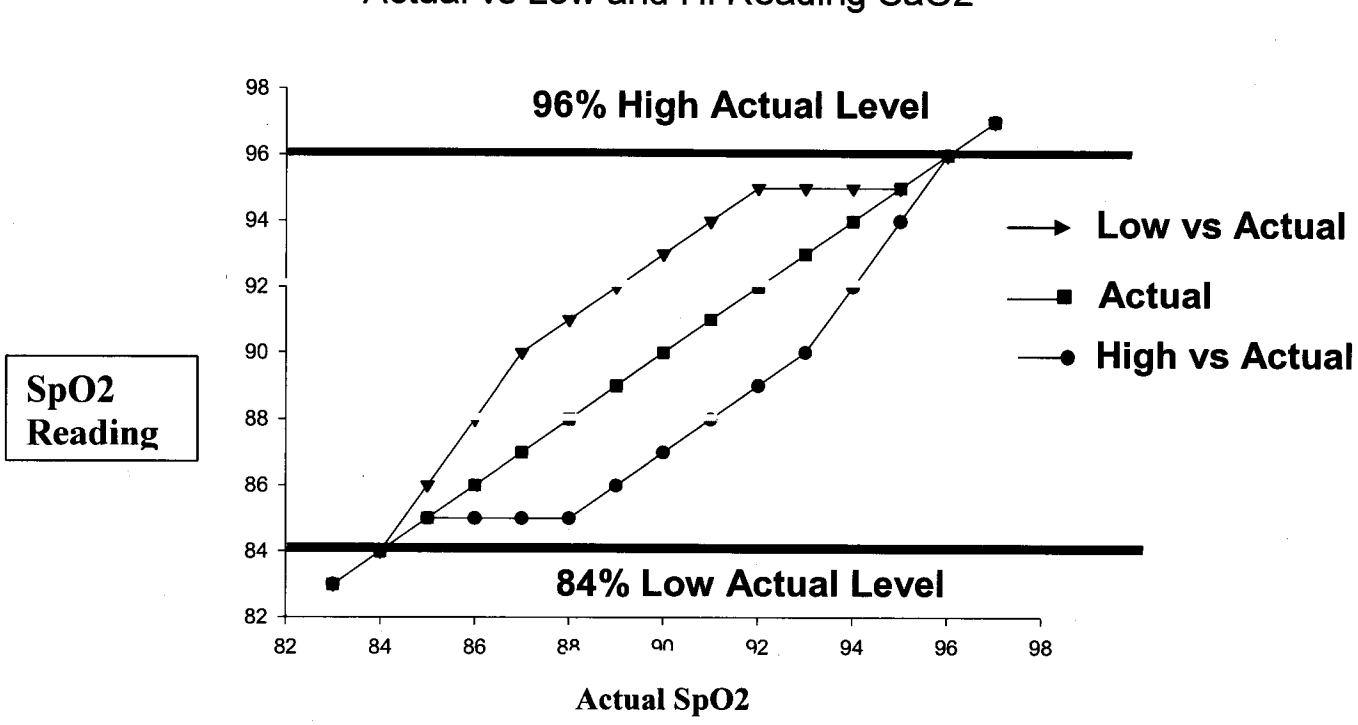
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarm Limits Will alarm above or below these values	Actual Alarm Values
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

In addition, and as an added safety issue, we will be asking the pulse oximeter provider to program the software of the actual pulse oximeters used in this trial to return to the actual reading when then the actual 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, ie < 85% and hyperoxia, ie SpO2 > 95%. An infant with an SpO2 outside these limits will have his/her actual SpO2 displayed on their pulse oximeter available for their caretakers to allow appropriate intervention. ***Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values***. We have asked the manufacturer to utilize the averaging algorithm of 16 seconds in keeping with current clinical practice. Some network centers use an averaging interval of 30 seconds. This averaging time will permit the change in reading from the altered readings to the actual SpO2 values without unmasking the caretakers.

We believe that this methodology will reassure all caretakers, and provide an acceptable ethical design for this trial. In addition we are confident that caretakers will not be aware of the shift from altered SpO2s to actual values, as few if any caretakers actually watch the changes in SpO2 but are alerted to do so by alarms. Thus in most circumstances by the time the caretaker responds to an alarm, the change from altered to actual SpO2 will have, in most circumstances, already occurred. 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 96% which will ensure that the infants SpO2 will be separated throughout this range.


Actual vs Low and Hi Reading SaO2
96% High Actual Level
84% Low Actual Level
Low vs Actual
Actual
High vs Actual
SpO2 Reading
Actual SpO2
98
96
94
92
90
88
86
84
82
82
84
86
88
90
92
94
96
98

At 3 days and every subsequent 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per each second of monitoring for a 72 hour period), from the study pulse oximeters will be downloaded and transmitted without further review or analyses 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 28 days 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 and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a device called a "NeoPuff®" or an equivalent device (See **3.6**). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece to allow the resuscitator to set both the Peak Inspiratory Pressure (PIP) and the PEEP or CPAP level, and to control the rate of ventilation. This device can also deliver CPAP

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.[555657]. 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.[58]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

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 (**See Section 4.1**)
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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[59]
4. Death

4.5 Resuscitation Associated Events

Resuscitation associated events will be noted and may include:

1. Significant bradycardia secondary to trigeminal stimulation
2. Significant gastric distension thought to be secondary to excessive airway pressure

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, ROP
- 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

6.1 Training Study Personnel

A training video on the use of the Neopuff or equivalent device, and the set-up and use of the video recording apparatus will be distributed to sites for review before the training site visit. The site visit by the PI and representatives from Fisher-Paykel (distributors of Neopuff) to install the equipment and in-service the Neopuff and the Bubbleflow for CPAP(if available). Training will be provided as well as a detailed protocol for obtaining and transmitting the stored PO SpO2 and Heart rate data.

6.1.1 Job Descriptions of Study Personnel

The NICHD Coordinators will assist the Respiratory therapists in each unit regarding the set up the Neopuff equipment and bubbleflow apparatus (if utilized for CPAP – currently not FDA approved).

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during a dedicated training meeting. In addition the study staff will have extensive in-service regarding the study POs utilized.

6.1.3 Training Materials and Certification

A training video to review the set-up of the Neopuff, and the bubbleflow will be distributed and sites will be certified on the use of the Neopuff, and bubbleflow apparatus.

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR COT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes were calculated from the GDB:

--BPD/Mortality—67%
--ROP ≥ 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		
		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. On site monitoring will be performed by an initial site visit, review of the data forms, and independent review of the video recordings, which contain the entire randomized elements of this study. Protocol violations will be reviewed, and if frequent, will 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 infants 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				

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

52 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

53 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

54 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

55 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

56 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

57 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

58 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

59 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From:	Neil Finer
To:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"
Cc:	Hastings, Betty J.; Poole, W. Kenneth
Date:	Friday, March 12, 2004 7:38:37 PM
Attachments:	COT Trial March 11final 04.doc

Hello Everyone
Here is the final version. I think that this is ready for the production of the Study manual. Wade Rich will work with Betty and others.
I tried to call Rose today. Rose, we would like to pursue the pilot that Wally developed and sent you. I think that the 5 centers are ready to submit to the IRB, This would allow testing of the altered POs well as the evaluation of the stored PO data that will be part of the COT trial. The only possibly unfinished task is the renaming. If Av and Wally and others want to provide suggestions, we could consider a change.
I suspect that no one will really care.
Be well
Neil

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Cc: Wally Carlo
Subject: RE: COT ?Final Protocol
Date: Friday, March 12, 2004 7:52:35 PM
Attachments: COT Trial March 11final 04.doc

Hi Rose
I tried to call you today. I am on service and have been unable to leave the NICU. Here is the final. We have reviewed and it looks good. I have sent to Betty and Ken as well.
Can we move ahead with Wally's pilot which will confirm the PO offsets and test the way we will collect that information? Wade has already talked with Betty regarding the manual.
Thanks
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, March 12, 2004 6:28 AM
To: 'nfiner@ucsd.edu'
Subject: RE: COT ?Final Protocol

Neil
Can I send this to betty Hastings at rti or do you anticipate further changes - I would like her to get started ASAP on the manual of operations and updating the forms from the pilot study.
Thanks
rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, March 11, 2004 9:29 PM
To: Ed Donovan; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.
Subject: COT ?Final Protocol

Hello Everyone
I am trying to keep my promise that this protocol will be good to go before mid-March
I am attaching the most current Mar 11 Version. Please give it a final look. I have made a few more changes based on some critiques that I have received.
I have copied below the new or changed areas.
I have called the groups CPAP and Early surfactant

: **Surfactant**

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant

Extubation:

Extubation ***MUST*** be attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 ≤ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks.
Extubation without meeting these criteria will be considering a protocol violation.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

Note that I have used an SpO2 of 88% as the criteria as this is the low end of the target range and is more consistent with our use of these ranges.

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarm Limits Will alarm above or below these values	Actual Alarm Values
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

This is a correction as the alarms will actually sound at 84% and 96%

Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values

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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

In addition I have attached the actual pulse oximeter outputs as tested by Masimo. These look OK to us. Your thoughts??
I will be in Australia next week, so I will check back with you in a week. Please let Rose know if we can proceed with this version. In addition, I would like to have Wally's pilot for the POs approved so that the 5 sites can begin. I have asked Masimo for 20-25 test devices.
Be well
Neil

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD)
Cc:	Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.
Subject:	SUPPORT Protocol
Date:	Tuesday, March 16, 2004 9:29:40 PM
Attachments:	SUPPORT Trial March 17.doc

Hello Rose
I sense that we have support for the SUPPORT Protocol.
I have attached with the name change and minor updates. Wade has already begun the manual with Betty.
I have a question for all sites - Please help me define hemodynamic stability - I will try to think up a working definition.
G'day mates
Neil

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 Of the NICHD Neonatal Research Network

Mar 17, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

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 ≥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. 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 COT 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.

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.[51] 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[52] using a 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.[53] 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 ($\leq$ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 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.[54] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for te 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 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 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 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 $\geq$ 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

Neopuff resuscitators, equivalent T-piece resuscitators or a Neonatal ventilator including disposable circuits, will be provided to all sites for delivery room management. Sites may use equivalent devices that are already available. A training video to explain the proper use of the Neopuff® will be provided to each site in advance of a site visit. If available CPAP will be provided by the Bubbleflow device (Fisher&Paykel, Auckland, NZ). This device is currently under FDA consideration. We may apply for an IDE to use this device for this trial if it has not received FDA approval prior to trial initiation

3.7 Randomization

Gestation-specific, stratified. Randomization 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 are being randomized to different treatment arms.

Each randomization will indicate randomization to either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and to 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 1 hour following NICU admission.

CPAP Group : Early Extubation and CPAP – Both Strata

Delivery Room Management

FiO2:

Infants will be resuscitated using whatever FiO_2 represents current practice in each unit

CPAP:

CPAP or positive pressure ventilation with PEEP utilized if the infant requires positive pressure ventilation, PPV during resuscitation for stabilization. The CPAP is continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. The Neopuff® or equivalent (See Section **3.6**) will be used to deliver initial CPAP in the delivery room.

It is acceptable to insert nasal prongs in the delivery room and transport on such a device with CPAP or PPV/PEEP to the NICU.

Intubation:

Infants who require intubation for resuscitation will receive surfactant in the DR area at the discretion of the attending physician, or once in the NICU, with the recommendation that such surfactant be given within 30 $\pm$30 min minutes of birth for infants who required DR intubation.

Thus earlier 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. This was the approach used for the DR CPAP feasibility trial.

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice, apart from the restriction that treatment infants may not be intubated for sole purpose of giving surfactant in the delivery room (DR).

NICU Management

These infants will be managed on nasal CPAP, and 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:

CPAP-Treatment infants may only be intubated if they meet ANY of these criteria and given surfactant (within the first 48 hours of life in the presence of respiratory distress)

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

Extubation:

An intubated Treatment infant *MUST have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable

These criteria will continue in effect for 14 days of life for 24-25 weeks and 7 days for 26-27 weeks.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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- Early Surfactant Group: Prophylactic/Early Surfactant and Ventilation

Overview:
Control infants are to be treated using an approach considered similar to current standards of care. The requirements for intubation of such infants are based on the best evidence to date suggesting that prophylactic surfactant by 15 minutes or early surfactant within 2 hours of birth provide a significant survival benefit. This approach will be used for all infants in the all Control Infants in both strata.

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.

Delivery Room Management :
Infants will be intubated in the delivery room and given surfactant or receive surfactant within 30 $\pm$ 30 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:
Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**
Extubation ***MUST*** be attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 $\leq$ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to attempt to extubate an infant meeting all of the above 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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous..

The protocol will require that all eligible infants in the Control stratum are intubated and receive prophylactic/early surfactant.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks.

For all Infants, Both Strata

For any infant in any arm of this trial, 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. All the above criteria will be in effect for the first 14 days of life for the 24 to 25 6/7ths week stratum and 7 days for the 26 to 276/7ths week stratum, following which current unit practice will dictate management.

The protocol requires that surfactant be administered to any infant intubated within 48 hours of birth, who has not previously received surfactant.

Repeat surfactant dosing should follow the manufacturers' recommendations for dose and interval, and criteria are indicated in the protocol. Repeat dosing is not required by the study protocol.

There is no requirement for the use of caffeine and its use should follow center

practice. Similarly indomethacin use will follow current center practice.

Nasal SIMV may be used for any infant in the trial *only following extubation*. It may not be used for Treatment infants randomized to receive CPAP, who have not been intubated. In addition the above intubation criteria will apply to all infants irrespective of whether they are receiving Nasal SIMV.

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) 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 94%. 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 gradually 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 following NICU admission, with a maximal allowable delay of 60 minutes. 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% to 95% for both groups. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

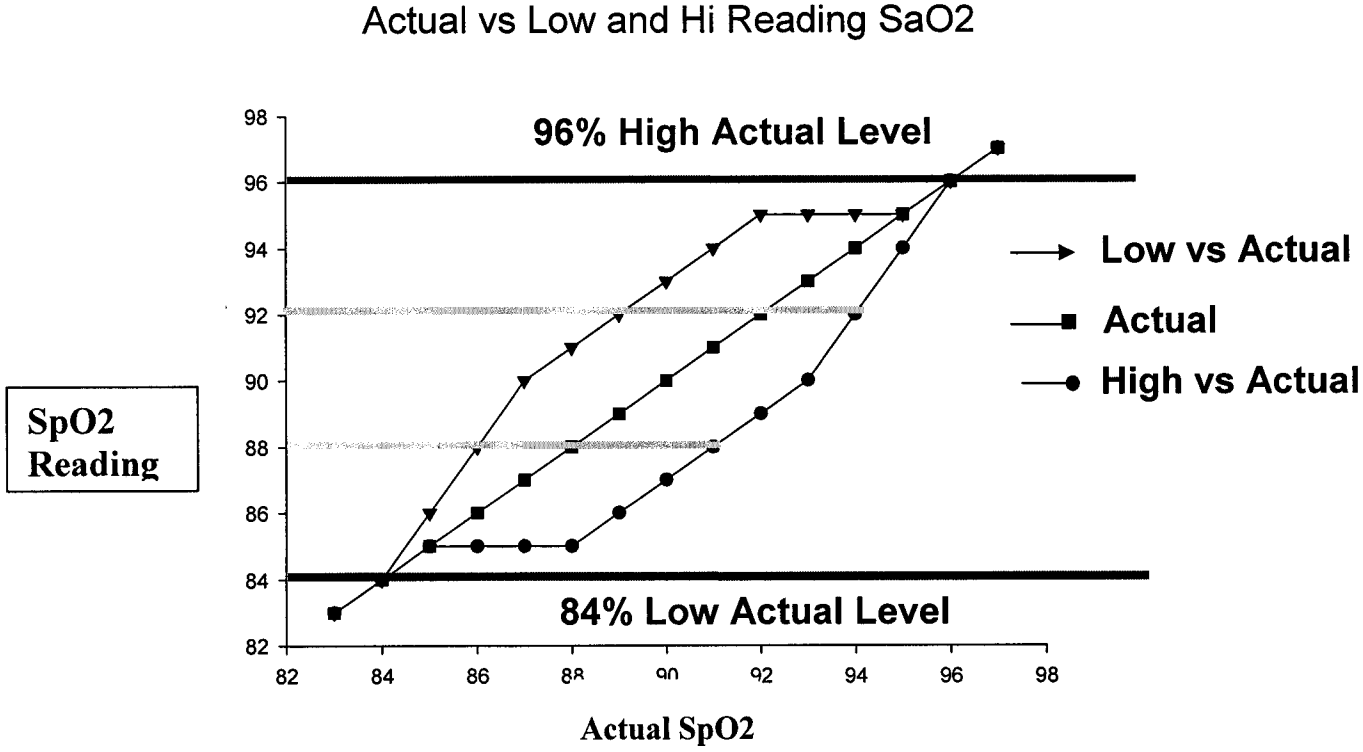
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

Table. Output and Actual SpO2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarm Limits Will alarm above or below these values	Actual Alarm Values
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

In addition, and as an added safety issue, we will be asking the pulse oximeter provider to program the software of the actual pulse oximeters used in this trial to return to the actual reading when then the actual 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, ie < 85% and hyperoxia, ie SpO2 > 95%. An infant with an SpO2 outside these limits will have his/her actual SpO2 displayed on their pulse oximeter available for their caretakers to allow appropriate intervention. ***Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values***. We have asked the manufacturer to utilize the averaging algorithm of 16 seconds in keeping with current clinical practice. Some network centers use an averaging interval of 30 seconds. This averaging time will permit the change in reading from the altered readings to the actual SpO2 values without unmasking the caretakers.

We believe that this methodology will reassure all caretakers, and provide an acceptable ethical design for this trial. In addition we are confident that caretakers will not be aware of the shift from altered SpO2s to actual values, as few if any caretakers actually watch the changes in SpO2 but are alerted to do so by alarms. Thus in most circumstances by the time the caretaker responds to an alarm, the change from altered to actual SpO2 will have, in most circumstances, already occurred. 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 96% which will ensure that the infants SpO2 will be separated throughout this range.


Actual vs Low and Hi Reading SaO2
96% High Actual Level
84% Low Actual Level
Low vs Actual
Actual
High vs Actual
SpO2 Reading
Actual SpO2
98
96
94
92
90
88
86
84
82
82
84
86
88
90
92
94
96
98

Every 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) from the study pulse oximeters will be downloaded and transmitted without further review or analyses 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 28 days 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 and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a device called a "NeoPuff®" or an equivalent device (See **3.6**). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece to allow the resuscitator to set both the Peak Inspiratory Pressure (PIP) and the PEEP or CPAP level, and to control the rate of ventilation. This device can also deliver CPAP

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.[555657]. 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.[58]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

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 (**See Section 4.1**)
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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[59]
4. Death

4.5 Resuscitation Associated Events

Resuscitation associated events will be noted and may include:
1. Significant bradycardia secondary to trigeminal stimulation
2. Significant gastric distension thought to be secondary to excessive airway pressure

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, ROP
- 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

6.1 Training Study Personnel

A training video on the use of the Neopuff or equivalent device, and the set-up and use of the video recording apparatus will be distributed to sites for review before the training site visit. The site visit by the PI and representatives from Fisher-Paykel (distributors of Neopuff) to install the equipment and in-service the Neopuff and the Bubbleflow for CPAP(if available). Training will be provided as well as a detailed protocol for obtaining and transmitting the stored PO SpO2 and Heart rate data.

6.1.1 Job Descriptions of Study Personnel

The NICHD Coordinators will assist the Respiratory therapists in each unit regarding the set up the Neopuff equipment and bubbleflow apparatus (if utilized for CPAP – currently not FDA approved).

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during a dedicated training meeting. In addition the study staff will have extensive in-service regarding the study POs utilized.

6.1.3 Training Materials and Certification

A training video to review the set-up of the Neopuff, and the bubbleflow will be distributed and sites will be certified on the use of the Neopuff, and bubbleflow apparatus.

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR COT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes were calculated from the GDB:

--BPD/Mortality—67%
--ROP ≥ 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		
		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. On site monitoring will be performed by an initial site visit, review of the data forms, and independent review of the video recordings, which contain the entire randomized elements of this study. Protocol violations will be reviewed, and if frequent, will 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 infants 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				

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

52 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

53 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

54 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

55 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

56 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

57 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

58 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

59 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From: Higgins, Rosemary (NIH/NICHD)
To: "bkh@rti.org"
Subject: Fw: SUPPORT Protocol
Date: Wednesday, March 17, 2004 7:12:54 AM
Attachments: SUPPORT Trial March 17.doc

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: Wade Rich <wrich@ucsd.edu>; Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@PEDS.UAB.EDU>; Shahnaz Duara <sduara@miami.edu>; Ed Donovan <Edward.Donovan@cchmc.org>; Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>
Sent: Tue Mar 16 21:17:57 2004
Subject: SUPPORT Protocol

Hello Rose
I sense that we have support for the SUPPORT Protocol.
I have attached with the name change and minor updates. Wade has already begun the manual with Betty.
I have a question for all sites - Please help me define hemodynamic stability - I will try to think up a working definition.
G'day mates
Neil

From: Wally Carlo, M.D.
To: "Neil Finer"; Higgins, Rosemary (NIH/NICHD)
Cc: Wade Rich
Subject: RE: SUPPORT Protocol
Date: Wednesday, March 17, 2004 7:36:58 AM

Neil: I am trying to quote your 2003 PAS abstract on the DR CPAP pilot. As it is not in the book, do you know how to cite the reference? Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, March 16, 2004 8:18 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.
Subject: SUPPORT Protocol

Hello Rose
I sense that we have support for the SUPPORT Protocol.
I have attached with the name change and minor updates. Wade has already begun the manual with Betty.
I have a question for all sites - Please help me define hemodynamic stability - I will try to think up a working definition.
G'day mates
Neil

Incoming mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.593 / Virus Database: 376 - Release Date: 2/20/2004

Outgoing mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.593 / Virus Database: 376 - Release Date: 2/20/2004

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT budget
Date: Tuesday, March 23, 2004 1:41:39 PM
Attachments: Support DRCPAP 2004 A budget.xls

I renamed this file but here is the DRCPAP budget, funded in FY01B. This awarded the pilot and the study.

I have a close out of the pilot as a separate file. I thought you send Heart Blood and Lung a Budget for the trial. Please advise.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

FY2041- A Support DR CPAP DRAFT BUDGET															
	Estimated # Pilot patients	PILOT Start-up	Equipment	Supplies	Data collection (4hrs@$32/hr)	subtotal direct pilot	Start-up + training	TRIAL Estimated umber of total pts	Equipment	Supplies	*Ventilation* Data collection @$1000/pt	Total direct	Indir Factor	Indirect $$	2001-B TOTAL
Case*	20	2000	$5,000	$500	$2,560	$10,060	$2,000	33			$33,000	$43,060	0.53	$22,822	$65,882
Texas-Hstn							$2,000	40	$5,000	$500	$40,000	$45,500	0.495	$22,523	$68,023
Texas-Dls							$2,000	28	$5,000	$500	$28,000	$33,500	0.56	$18,760	$52,260
Wayne St							$2,000	33	$5,000	$500	$33,000	$38,500	0.49	$18,865	$57,365
Miami*	30	2000	$5,000	$500	$3,840	$11,340	$2,000	45			$45,000	$56,340	0.515	$29,015	$85,355
Emory							$2,000	28	$5,000	$500	$28,000	$33,500	0.28	$9,380	$42,880
Cincinnati*	25	2000	$5,000	$500	$3,200	$10,700	$2,000	40			$40,000	$50,700	0.53	$26,871	$77,571
Indiana							$2,000	40	$5,000	$500	$40,000	$45,500	0.49	$22,295	$67,795
Yale							$2,000	13	$5,000	$500	$13,000	$18,500	0.299	$5,532	$24,032
Brown							$2,000	33	$5,000	$500	$33,000	$38,500	0.393	$15,131	$53,631
Stanford							$2,000	18	$5,000	$500	$18,000	$23,500	0.6	$14,100	$37,600
Alabama*	35	2000	$5,000	$500	$4,480	$11,980	$2,000	50			$50,000	$61,980	0.435	$26,961	$88,941
WFU							$2,000	48	$5,000	$500	$48,000	$53,500	0.45	$24,075	$77,575
Duke							$2,000	33	$5,000	$500	$33,000	$38,500	0.54	$20,790	$59,290
Rochester							$2,000	28	$5,000	$500	$28,000	$33,500	0.595	$19,933	$53,433
UCSD*	40	2000		$500	$5,120	$7,620	$2,000	50			$50,000	$57,620	0.515	$29,674	$87,294
Totals	150		**$20,000**	**$2,500**	**$19,200**	**$51,700**	**$32,000**	560	**$55,000**	**$5,500**		**$672,200**		**$326,726**	**$998,926**

*Pilot enters; funds for all other centers restricted

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT budget
Date: Tuesday, March 23, 2004 1:47:23 PM

Great!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 23, 2004 1:46 PM
To: 'petrie@rti.org'
Subject: Re: SUPPORT budget

For the pilot, we willwait for the sc!

I also talked to Jon Tyson and he told me they would get the us's to rti.

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Petrie, Carolyn <petrie@rti.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Mar 23 13:44:52 2004
Subject: RE: SUPPORT budget

Do you need a draft budget prepared or just wait until SC?

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, March 23, 2004 1:44 PM
To: 'petrie@rti.org'
Subject: Re: SUPPORT budget

I'll look at this later thid week.
They also have a "new pilot" to test the oximeters that they want to use prior to the main study starting - the steering committee will need to discuss
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Petrie, Carolyn <petrie@rti.org>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
Sent: Tue Mar 23 13:40:59 2004
Subject: SUPPORT budget

I renamed this file but here is the DRCPAP budget, funded in FY01B. This awarded the pilot and the study.

I have a close out of the pilot as a separate file. I thought you send Heart Blood and Lung a Budget for the trial. Please advise.

Carolyn Petrie

Neonatal Research Network Coordinator

RTI International

6110 Executive Blvd

Suite 420

Rockville, MD 20852

ph. (301) 230-4648

fx. (301) 230-4646

From:	Neil Finer
To:	Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"
Date:	Tuesday, March 23, 2004 7:51:04 PM
Attachments:	SUPPORT Trial March 23 final.doc

Hello Everyone
I will be missing the next Steering Committee and Wally will be presenting the SUPPORT trial and the PO Pilot. I am attaching the revision of the SUPPORT Trial in which I have made a Chart at the end of the protocol. This simplifies the Protocol and may be an ideal single sheet to circulate at the Steering Committee for explanation. It was suggested that we prepare such a Table by Bill Benitz and I think that it was a great idea.
Please review and let me know if this looks OK. I have simplified the protocol explanations and made a few minor changes. One major change is the requirement that the PO arm begin at 2 hours or less. I was under the impression that POST ROP would begin close to birth, but at the meeting in Australia it was clear that this is more of a first 24 hours issue. As a result I would like to make it easier on the sites to give the surfactant etc and stabilize the infant and not be rushed to get the PO on. I would appreciate your thoughts as to this suggestion.
Look forward to your thoughts.
Be well
Neil

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 of the NICHD Neonatal Research Network

Mar 17, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

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 ≥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. 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 COT 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 ≥ 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.

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.[51] 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[52] using a 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.[53] 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 of 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.[54] 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 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 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 $\geq$ 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

Neopuff resuscitators, equivalent T-piece resuscitators or a Neonatal ventilator including disposable circuits, will be provided to all sites for delivery room management. Sites may use equivalent devices that are already available. A training video to explain the proper use of the Neopuff® will be provided to each site in advance of a site visit. If available CPAP will be provided by the Bubbleflow device (Fisher&Paykel, Auckland, NZ). This device is currently under FDA consideration. We may apply for an IDE to use this device for this trial if it has not received FDA approval prior to trial initiation

3.7 Randomization

Gestation-specific, stratified. Randomization 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 are being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate randomization to either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and to 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 1 hour 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 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) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation as noted above on page 13)

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 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 $\leq$ 15 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).

These criteria will continue in effect for 14 days of life for 24-25 weeks and 7 days for 26-27 weeks.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

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:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

An intubated Surfactant-Control infant **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 $\leq$ .40 with a SpO2 > 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to attempt to extubate an infant meeting all of the above 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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%

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 for 24-25 weeks and 7 days from birth for 26-27 weeks.

Failure to intubate on infant meeting both of these criteria will be recorded as a study protocol violation unless extenuating circumstances are noted.

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic/early surfactant for all Control infants, but allows the surfactant to be delayed for up to 60 minutes in recognition of the practice patterns at some Network units and the lack of good prospective comparative data that demonstrate that such a delay is disadvantageous.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days for infants of 24-25 weeks and 7 days from birth for infants of 26-27 weeks.

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 gradually 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 following NICU admission, with a maximal allowable delay of 120 minutes. 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% to 95% for both groups. 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 CRT output will be the same in both groups (Table).

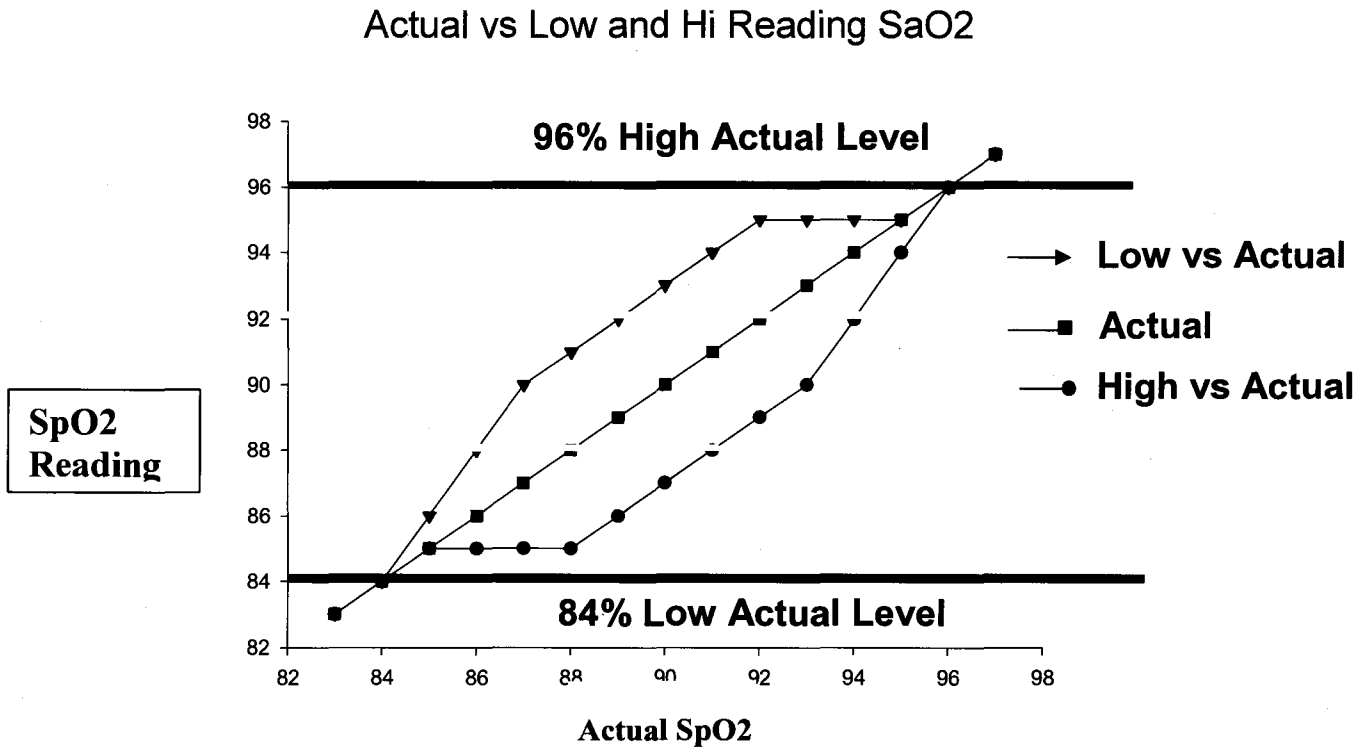
Table. Output and Actual SpO2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarm Limits Will alarm above or below these values	Actual Alarm Values
Low SpO2 range group	88-92%	85-89%	85-95%	84-96%
High SpO2 range group	88-92%	91-95%	85-95%	84-96%

In addition, and as an added safety issue, we will be asking the pulse oximeter provider to program the software of the actual pulse oximeters used in this trial to display the actual reading when then the actual 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, ie < 85% and hyperoxia, ie SpO2 > 95%. An infant with an SpO2 outside these limits will have his/her actual SpO2 displayed on their pulse oximeter available for their caretakers to allow appropriate intervention. ***Thus, the alarms will be activated above 95% or below 85%, which will result in the units alarming for real SpO2 values as the values above 95% and below 85% are actual values***. We have asked the manufacturer to utilize the averaging algorithm of 16 seconds in keeping with current clinical practice. Some network centers use an averaging interval of 30 seconds. This averaging time will permit the change in reading from the altered readings to the actual SpO2 values without unmasking the caretakers.

We believe that this methodology will reassure all caretakers, and provide an acceptable ethical design for this trial. In addition we are confident that caretakers will not be aware of the shift from altered SpO2s to actual values, as few if any caretakers actually watch the changes in SpO2 but are alerted to do so by alarms. Thus in most circumstances by the time the caretaker responds to an alarm, the change from altered to actual SpO2 will have, in most circumstances, already occurred. 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 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) from the study pulse oximeters will be downloaded and transmitted without further review or analyses 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.

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 device called a "NeoPuff®" or an equivalent device (See **3.6**). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece to allow the resuscitator to set both the Peak Inspiratory Pressure (PIP) and the PEEP or CPAP level, and to control the rate of ventilation. This device can also deliver CPAP.

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.[555657]. 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.[58]

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.

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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[59]
4. Death

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, ROP
- 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

6.1 Training Study Personnel

A training video on the use of the Neopuff or equivalent device, and the set-up and use of the video recording apparatus will be distributed to sites for review before the training site visit. The site visit by the PI and representatives from Fisher-Paykel (distributors of Neopuff) to install the equipment and in-service the Neopuff and the Bubbleflow for CPAP(if available). Training will be provided as well as a detailed protocol for obtaining and transmitting the stored PO SpO2 and Heart rate data.

6.1.1 Job Descriptions of Study Personnel

The NICHD Coordinators will assist the Respiratory therapists in each unit regarding the set up the Neopuff equipment and Bubbleflow apparatus (if utilized for CPAP – currently not FDA approved).

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during a dedicated training meeting. In addition the study staff will have extensive in-service regarding the study POs utilized.

6.1.3 Training Materials and Certification

A training video to review the set-up of the Neopuff, and the bubbleflow will be distributed and sites will be certified on the use of the Neopuff, and bubbleflow apparatus.

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
10% (multiples to same arm)	1120	1310	1456	1704
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

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. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering. Thus the actual sample size for this trial would be 1310 for 80% power. These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1310 infants, adding 15% attrition factor for a total of 1506 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR COT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes were calculated from the GDB:

--BPD/Mortality—67%
--ROP ≥ 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
Yes	45	55	50
No	55	45	60
Overall	50	60	55

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

CPAP	Low	High	Overall
Yes	55	55	55
No	65	65	65
Overall	60	60	60

Table IIA

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

SpO2

CPAP	Low	High	Overall
Yes	25	35	30
No	35	45	40
Overall	30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	35	45	40
	No	35	45	40
	Overall	35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and CPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
CPAP	Yes	40	50	45
	No	50	60	55
	Overall	45	55	50

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. On site monitoring will be performed by an initial site visit, review of the data forms, and independent review of the video recordings, which contain the entire randomized elements of this study. Protocol violations will be reviewed, and if frequent, will 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 infants 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				

Treatment Group	Early CPAP/Early Extubation	Prophylactic Surfactant
Gestational Age Stratum	24-25 Weeks + 26-27 weeks	24-25 Weeks + 26 – 27 weeks
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** **If intubated, give surfactant within the first 48 hours of life in the presence of respiratory distress** • FiO_2 >.50 required to maintain indicated SpO2 ≥ 88% (using the altered Pulse Oximeters) for one hour • Arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if PvCO2 > 70 torr) for 2 successive gases ≥ 15 minutes apart. • Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.	**Reintubation Criteria** **Intubate** if both criteria met for >4 hours. **May** intubate for less severe criteria • $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) • An FiO2 > .40 with or without CPAP to maintain an SpO2 < 88%
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% • A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV) • 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 ≤ .40 with SpO2 > 88% using the study oximeter • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate ≤ 15 bpm, amplitude < 2X MAP on high frequency ventilation (HFO) • Absence of clinically significant PDA

Repeated Surfactant Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
CPAP Discontinuation	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Study Criteria in PNAge(days)	14 days	7 days

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

52 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

53 Good, W. V.; Hardy, R. J.; Dobson, V.; Palmer, E. A.; Phelps, D. L.; Quintos, M.; et al. Revised indications for the treatment of retinopathy of prematurity - Results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology. 2003; 121(12):1684-1696

54 Cole CH, Wright, KW, Tarnow-Mardi, W, Phelps, DL. Resolving our uncertainty about oxygen. Pediatrics 2003;112:1415-1419

55 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

56 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

57 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

58 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

59 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams J Pediatr 1978;92:529-34

From: Higgins, Rosemary (NIH/NICHD)
To: "BKH@RTI.ORG"
Subject: Fw:
Date: Tuesday, March 23, 2004 8:43:55 PM
Attachments: SUPPORT Trial March 23 final.doc

Betty
I am out of the office and not able to open this. I hope there are not significant changes.
Rose

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Shahnaz Duara <sduara@miami.edu>; Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>; Ed Donovan <Edward.Donovan@chmcc.org>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Neil Finer <nfiner@ucsd.edu>; 'Wade Rich' <wrich@ucsd.edu>
Sent: Tue Mar 23 19:50:37 2004
Subject:

Hello Everyone

I will be missing the next Steering Committee and Wally will be presenting the SUPPORT trial and the PO Pilot. I am attaching the revision of the SUPPORT Trial in which I have made a Chart at the end of the protocol. This simplifies the Protocol and may be an ideal single sheet to circulate at the Steering Committee for explanation. It was suggested that we prepare such a Table by Bill Benitz and I think that it was a great idea.

Please review and let me know if this looks OK. I have simplified the protocol explanations and made a few minor changes. One major change is the requirement that the PO arm begin at 2 hours or less. I was under the impression that POST ROP would begin close to birth, but at the meeting in Australia it was clear that this is more of a first 24 hours issue. As a result I would like to make it easier on the sites to give the surfactant etc and stabilize the infant and not be rushed to get the PO on. I would appreciate your thoughts as to this suggestion.

Look forward to your thoughts.

Be well

Neil

From:	Neil Finer
To:	Das, Abhik; mcw3@cwru.edu; William Oh2 (WOh@wihri.org); sshankar@med.wayne.edu; Walid.Salhab@UTsouthwestern.edu; wcarlo@peds.uab.edu; sduara@miami.edu; goldb008@mc.duke.edu; richard.ehrenkranz@yale.edu; moshea@wfubmc.edu; jon.e.tyson@uth.tmc.edu; jlemons@iupui.edu; edward.donovan@chmcc.org; dstevenson@stanford.edu; dale_phelps@urmc.rochester.edu; [SCRN] Stoll, Barbara; aaf2@cwru.edu; Jobea0@chmcc.org; alaptook@WIHRI.org; Poole, W. Kenneth; Petrie, Carolyn
Cc:	Neil Finer; wrich@ucsd.edu; Petrie, Carolyn; Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD)
Subject:	Re: COT Trial Jan 20 04
Date:	Friday, January 23, 2004 3:42:59 PM
Attachments:	Ventilation Interventions.doc COT-Schema - Steering Comm Revision 04.ppt

We have made changes to simplify the protocol and hopefully allow a better understanding of the interventions. We are sending only the actual intervention for the ventilation arm and 2 PowerPoint slides for discussion at the Steering Committee.
Regards
See you next week
Neil
----- Original Message -----
From: "Petrie, Carolyn" <petrie@rti.org>
To: "Poole, W. Kenneth" <poo@rti.org>; <alaptook@WIHRI.org>; <Jobea0@chmcc.org>; <aaf2@cwru.edu>; "[SCRN] Stoll, Barbara" <barbara_stoll@oz.ped.emory.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>; <richard.ehrenkranz@yale.edu>; <goldb008@mc.duke.edu>; <sduara@miami.edu>; <wcarlo@peds.uab.edu>; <Walid.Salhab@UTsouthwestern.edu>; <sshankar@med.wayne.edu>; "William Oh2 (WOh@wihri.org)" <WOh@WIHRI.org>; <mcw3@cwru.edu>; "Das, Abhik" <adas@rti.org>
Cc: <higginsr@mail.nih.gov>; <nfiner@ucsd.edu>; "Hastings, Betty J." <bkh@rti.org>; "Petrie, Carolyn" <petrie@rti.org>
Sent: Wednesday, January 21, 2004 6:41 AM
Subject: COT Trial Jan 20 04

>
> Dear NRN Steering Committee-
>
> Please find the updated COT Trial protocol and responses to external
> reviews, attached.
>
> Thank you,
> Carolyn
>
>

COT Trial – Treatment Infants 24-25 6/7ths and 26-27 6/7ths

Delivery Room Management

DR CPAP

NICU Management

Intubation Criteria

Any of

FiO2 >.50 for SpO2 ≤ 90%
pH < 7.20 or PaCO2 > 65 torr
Hemodynamic instabilty

Must have *Extubation* attempted
Within 24 hrs if all following criteria met

PaCO2 < 65 torr and pH < 7.20
MAP < 10 cmH20 Rate < 15 bpm
Amp < 2X MAP if HiFi
SpO2≥90 with FiO2 < 50
Hemodynamically Stable

Criteria apply for first 14 days of life for 24-25 weeks and 7 days for 26-27 weeks

COT Trial – Control Infants
24-25 6/7ths and 26-27 6/7ths

Delivery Room Management
Prophylactic Surfactant <30+/- 15 min

NICU Management
Extubation Criteria

All of

> 48 hrs of age (24-25wk)
FiO2 <.40 for SpO2 ≤ 90%
pH > 7.30 or PaCO2 < 50 torr
MAP < 8 cm H20 Rate < 15 bpm, If
HiFi Amp < 2X MAP
Hemodynamic stabilty
No significant PDA

Must RE-intubate if
PaCO2 > 55 torr and
FiO2 ≥ .40 for SpO2 ≥ 90%
for > than 4 hours

Criteria apply for first 14 days of life for 24-25 weeks and 7 days for 26-27 weeks

TREATMENT Group : Early Extubation and CPAP – Both Strata

Delivery Room Management

FiO2:

Infants will be resuscitated using whatever FiO_2 represents current practice in each unit

CPAP:

CPAP or positive pressure ventilation with PEEP (if the infant requires positive pressure ventilation, PPV) until admission to the NICU using the Neopuff or equivalent device and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. The Neopuff® or equivalent (See Section **3.6**) will be used to deliver initial CPAP in the delivery room for infants randomized to the Early CPAP group, and may be used for resuscitation of the conventional group.

It is acceptable to insert nasal prongs in the delivery room and transport on such a device with CPAP or PPV/PEEP to the NICU.

Intubation:

Infants who require intubation for resuscitation will receive surfactant in the DR area at the discretion of the attending physician, or once in the NICU, with the recommendation that such surfactant be given within 30 $\pm$15 minutes of birth for infants who required DR intubation.

Thus earlier 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. This was the approach used for the DR CPAP feasibility trial.

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice, apart from the restriction that treatment infants may not be intubated for sole purpose of giving surfactant in the delivery room (DR).

NICU Management

These infants will be managed on nasal CPAP, or Nasal SIMV and may be intubated if they meet any of the criteria listed below. If intubated within the first 72 hours of life they should receive surfactant

Intubation:

Infants meeting the ANY of these criteria **MUST** be intubated and given surfactant (within the first 48 hours of life)

- An FiO_2 >.50 to maintain an indicated SpO2 $\geq$ 90% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for age and/or poor perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks..

(The average duration of ventilation of such infants is 6 days for all centers with a range of 2.8 to 8.1 days)

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation:

An intubated Treatment infant ***MUST have extubation attempted within 24 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 ≥ 90% with an FiO2 ≤ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable

These criteria will continue in effect for 14 days of life for 24-25 weeks and 7 days for 26-27 weeks.

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.

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

Surfactant

Infants intubated in the first 48 hours **MUST** be given 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 these 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 Group: Prophylactic Surfactant and Ventilation

Overview:

Control infants are to be treated using an approach considered similar to current standards of care. The requirements for intubation of such infants are based on the best evidence to date suggesting that prophylactic surfactant by 15 minutes or early surfactant within 2 hours of birth provide a significant survival benefit. This approach will be used for all infants in the all Control Infants in both strata.

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.

Delivery Room Management :

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 30 ±15 minutes of birth. They will be weighed on admission to the NICU. The other aspects of the resuscitation will be managed according to

the NRP guidelines and follow current center practice.

NICU Management:

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied:

***Extubation*:**

Extubation ***MUST*** be attempted if ***ALL*** of the following criteria are present

- Infant is > 48 hours of age for 24-25 weeks
- $PaCO_2$ < 50 torr and pH > 7.30(arterial or capillary samples)
- An FiO2 < .40 with a SpO2 > 90% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 24-25 weeks and 7 days from birth for 26-27 weeks..

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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study violation.

Reintubation:

Control Infants meeting **BOTH** of these criteria for more than 4 hours **MUST** be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 90% for a minimum of 30 minutes using the study pulse oximeters.

These criteria will continue in effect for a minimum of 14 days for 24-25 weeks and 7 days from birth for 26-27 weeks..

A Control infant who meets both criteria during the first 14 days of life **MUST** be intubated

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic surfactant for all Control infants, but allows the surfactant to be delayed for 45 minutes in recognition of the practice patterns at some Network units.

The protocol will require that all eligible infants in this stratum are intubated and receive prophylactic/early surfactant.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 7 days of life for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 7 days of life, apart from the use of CPAP/NSIMV and an FiO2 > 0.50.

For all Infants, Both Strata

For any infant in any arm of this trial, 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. All the above criteria will be in effect for the first 14 days of life for the 24 to 25 6/7ths week stratum and 7 days for the 26 to 276/7ths week stratum, following which current unit practice will dictate management.

Repeat surfactant dosing should follow the manufacturers' recommendations for dose and interval, and criteria are indicated in the protocol. Repeat dosing is not required by the study protocol.

From: Neil Finer
To: Petrie, Carolyn
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: CPAP conf call this Thurs.
Date: Monday, February 02, 2004 3:38:00 PM

Can we try for a meeting of those who could be there- I assume Wally, Ed me and Ken.
Regards
Neil

----- Original Message -----
From: Petrie, Carolyn
To: 'Neil Finer'
Cc: aRose Higgins (higginsr@mail.nih.gov)
Sent: Monday, February 02, 2004 11:59 AM
Subject: RE: CPAP conf call this Thurs.

Neil-

Looks like Shahnaz and Av are unable to attend. Ken is out until Wed. Let me know if we should query more formally.

carolyn

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 02, 2004 2:17 PM
To: Petrie, Carolyn
Subject: Re: CPAP conf call this Thurs.

Yes
Neil Finer

----- Original Message -----
From: Petrie, Carolyn
To: Poole, W. Kenneth ; M. D. Shahnaz Duara (sduara@miami.edu) ; M. D. Ed Donovan (edward.donovan@chmcc.org) ; M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu) ; M. D. Avroy A. Fanaroff (aaf2@cwru.edu)
Cc: aRose Higgins (higginsr@mail.nih.gov) ; M. D. Neil Finer (nfiner@ucsd.edu) ; Diane Timmer (Cincinnati) (diane.timmer@cchmc.org) ; Heidi Squibb (UCSD) (hsquibb@ucsd.edu) ; Marsha Sumner (UAB) (msumner@peds.uab.edu) ; (mlg@cwru.edu) ; Marsha Sumner (UAB) (msumner@peds.uab.edu) ; Hastings, Betty J. ; Petrie, Carolyn
Sent: Monday, February 02, 2004 9:07 AM
Subject: CPAP conf call this Thurs.

To the COT/CPAP subcommittee

Are you available for a CPAP conference call this Thursday (2/5) around 12pm EST (9am PST)?

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International

6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT presentation
Date: Friday, February 06, 2004 3:34:20 PM

Do you have Neil's COT presentation, sent after the SC meeting?

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Higgins, Rosemary (NIH/NICHD)
To: "Jon E Tyson"
Subject: RE: COT trial
Date: Friday, February 06, 2004 4:42:20 PM
Attachments: COT-Schema - Steering Comm Revision 04.ppt
COT Trial Jan 20 04.doc
Ventilation Interventions 1.20.04.doc

Jon
This is what I have - let me know if you needed something else.
Rose

-----Original Message-----
From: Jon E Tyson [mailto:Jon.E.Tyson@uth.tmc.edu]
Sent: Friday, February 06, 2004 4:38 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT trial

Neil said that he sent the revised protocol and power point slides out after the meeting for distribution from your office. If so, please forward.

Jon E. Tyson, MD, MPH
Center for Clinical Research and
Evidence-Based Medicine
6431 Fannin Street, MSB 2.106
Houston, TX 77030
Voice: 713-500-5651
Fax: 713-500-0519

From: Poole, W. Kenneth
To: "nfiner@ucsd.edu"
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: FW: Dr Finer"s Request...
Date: Tuesday, February 10, 2004 10:35:49 AM
Attachments: AdditionalManInfo(2-04).doc

The additional data you requested for the paper.

<<AdditionalManInfo(2-04).doc>>

Sarah Kandefer

Statistician

RTI International

3040 Cornwallis Rd.

PO Box 12194
RTP, NC 27709-2194

Ph: 919-485-7761

Fax:919-485-7762
email: skandefer@rti.org

Patient Description	**CPAP N = 55**	**CONTROL N = 49**
Gender – Males N (%)	31 (56%)	25 (51%)
Birth Weight (grams) ±SD	756 ± 196	789 ± 196
Gestational Age (Weeks) ±SD	25 ± 1.3	25 ± 1.2
Apgar 1 min ≤ 3 N (%)	25 (45%)	17 (35%)
Apgar 1 min ≤ 7 N (%)	43 (78%)	41 (84%)
Apgar 5 min < 3 N (%)	7 (13%)	5 (10%)
Apgar 5 min < 7 N (%)	25 (45%)	18 (37%)
Pneumothorax N (%) [1]	7 (13%)	4 (8.7%)
Antenatal Steroids given N (%)	54 (98%)	48 (98%)
Complete Steroid Course Given N (%)	22 (41%)	30 (63%)
Blood Gas Done after Admission N (%) [2]	50 (98%)	43 (91%)
Age at Blood Gas (Hours) ±SD	3.1 ± 5.5	1.6 ± 0.73
Blood Gas after Admission – pH Mean ± SD	7.2 ± 0.146	7.3 ± 0.09

Blood Gas after Admission – pCO_2 Mean ± SD	53 ± 14	47 ± 8.8
Blood Gas after Admission – pO_2 Mean ± SD	82 ± 62	69 ± 40
Blood Gas after Admission –HCO_3 Mean ± SD	21 ± 4.1	22 ± 3.2
Blood Gas after Admission – Base Mean ± SD	6.6 ± 5.3	4.4 ± 3.9
Blood Gas after Admission – FiO_2 Mean ± SD	0.54 ± 0.28	0.49 ± 0.22

[1] 2 CPAP and 3 Control infants died within 12 hours of life and do not have this diagnosis hence the denominators are 53 and 46, respectively

[2] 4 CPAP and 2 Control did not report whether a blood gas was done after admission or not, the data field is blank

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: complications
Date: Tuesday, February 10, 2004 12:44:03 PM
Attachments: com .xls

The data you requested. Please acknowledge receopt.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 05, 2004 4:04 PM
To: 'poo@rti.org'
Subject: complications

Ken
Can we get the incidence of complications for the last five years for infants < 1500 grams for
RDS
BPD
IVH
ROP
NEC
PDA
Sepsis (all - early + late)

I think Krisa had asked for some CV complications. this is for an NICHD/FDA initiative for BPCA (Best Pharmaceuticals Act for Children) to have drugs labeled with pediatric and neonatal indications.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

Incidence of comlications for GDB infants who survived 12 hours of life and born in 1998-2002.

Birth Year	1998	1999	2000	2001	2002	Total
Number	3317	3407	2975	3615	3402	16716
Comlications [N(%)]*						
RDS						
Req Oxygen 6-24 hrs of life	3311(54)	3400(52)	2946(53)	3603(58)	3387(54)	16647(54)
Clinical featur RDS within 24 hrs	3314(83)	3405(84)	2968(84)	3613(84)	3393(87)	16693(84)
Respiratory support till 24 hrs	3313(67)	3402(68)	2956(70)	3608(74)	3392(76)	16671(71)
Abnormal chest X-ray within 24 hrs	3311(72)	3403(74)	2966(72)	3598(73)	3382(76)	16660(73)
BPD	3041(21)	3117(23)	2729(25)	3451(24)	3223(23)	15561(23)
IVH 1	3048(11)	3153(9)	2743(11)	3363(10)	3164(10)	15471(10)
IVH II	3048(4)	3153(5)	2743(4)	3363(5)	3164(5)	15471(5)
IVH III	3048(7)	3153(7)	2743(7)	3363(9)	3164(9)	15471(8)
IVH IV	3048(6)	3153(5)	2743(6)	3363(6)	3164(7)	15471(6)
ROP	2118(50)	2206(50)	1963(52)	2426(47)	2358(46)	11071(49)
NEC	3315(6)	3406(7)	2975(7)	3615(8)	3397(7)	16708(7)
PDA	3314(27)	3405(30)	2974(29)	3615(34)	3393(33)	16701(31)
Early onset of septicemia	3314(2)	3403(2)	2973(1)	3613(2)	3392(2)	16695(2)
Late onset of Septicemia	3313(21)	3400(23)	2964(26)	3612(23)	3388(24)	16677(23)

* N is the denominator.

From: Poole, W. Kenneth
To: "nfiner@ucsd.edu"
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Sample size for COT
Date: Thursday, February 12, 2004 4:58:22 PM

Neil,

As I mentioned in an earlier e-mail, the sample sizes that now appear in the COT protocol were calculated assuming that babies would be randomized individually. If multiples are randomized to the same treatment then this introduces a clustering effect into the design and thereby increases the sample size required to achieve the same power as simple random sampling. Our analysis of the GDB data indicates that this "design effect" is about 1.12 so the sample sizes in the protocol would have to be increased by 12% to accommodate the clustering.

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Advisory board input for COT trial
Date: Friday, February 13, 2004 6:59:50 PM

Thanks Rose

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (E-mail) ; Carlo Waldemar (E-mail) ; Charles Rosenfeld ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Fanaroff Avroy (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; Michelle Walsh ; Neil Finer ; Oh William (E-mail) ; Poole Kenneth (E-mail) ; Ronald GOldberg ; Shahnaz Duara ; Shankaran Seetha (E-mail) ; Stevenson David (E-mail) ; Stoll Barbara (E-mail) ; Tyson Jon (E-mail) ; Walid Salhab (E-mail)
Cc: 'petrie@rti.org' ; 'bkh@rti.org'
Sent: Friday, February 13, 2004 1:36 PM
Subject: Advisory board input for COT trial

Hi,
I have responses from 5 of 6 advisory board members for the COT trial - 4 out of 5 agree that we should go forward with the trial. One member has some concerns that the subcommittee can address. Therefore we can plan on this trial going forward in the network based on this input from the advisory board and on the SC vote last month.
I am awaiting input from NHLBI regarding the potential for co-funding of the project.
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From:	Petrie, Carolyn
To:	Charles Rosenfeld (crosen@mednet.swmed.edu); Poole, W. Kenneth; M. D. Abbot Laptook (alaptook@WIHRI.org); [SCRN] Stoll, Barbara; M. D. Dale L. Phelps (dale_phelps@urmc.rochester.edu); M. D. David K. Stevenson (dstevenson@stanford.edu); M. D. James A. Lemons (jlemons@iupui.edu); M. D. Jon Tyson (jon.e.tyson@uth.tmc.edu); M. D. Michael O"Shea (moshea@wfubmc.edu); M. D. Richard Ehrenkranz (richard.ehrenkranz@yale.edu); M. D. Ronald Goldberg (goldb008@mc.duke.edu); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org); Das, Abhik
Cc:	Higgins, Rosemary (NIH/NICHD); M. D. Neil Finer (nfiner@ucsd.edu); Hastings, Betty J.
Subject:	COT Trial Presentation
Date:	Monday, February 16, 2004 1:42:15 PM
Attachments:	COT Trial - New Schema Feb 16 04.ppt

Please find the COT Trial presentation as prepared by Dr. Finer attached to this email. He made a very few modifications such as revising the sample size for multiples being randomized as a unit.

Thank you,
Carolyn

COT Trial - Ventilation Arm

- **Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic/early surfactant by 1 hour**

COT Trial – CPAP Treatment
24-25 6/7ths and 26-27 6/7ths weeks

Delivery Room Management

DR CPAP

NICU Management

May not intubate unless any of

- FiO2 >.50 for SpO2 ≤ 90%
- pH < 7.20 or PaCO2 > 65 torr
- Hemodynamic instability

COT Trial – CPAP Treatment
24-25 6/7ths and 26-27 6/7ths weeks

Must have *Extubation* attempted within 24 hrs if all following criteria met

- **$PaCO_2$ < 65 torr and pH > 7.20**
- **MAP < 10 cmH20 Rate ≤ 15 bpm**
- **Amp < 2X MAP if HiFi**
- **SpO_2 ≥ 90 with FiO_2 < .50**
- **Hemodynamically Stable**

Criteria apply for first 14 days of life for 24-25 weeks and 7 days for 26-27 weeks

COT Trial – Proph/Early Surf - Control 24-25 6/7ths and 26-27 6/7ths weeks

Delivery Room Management

Prophylactic/Early Surfactant < 30+/- 30 min

NICU Management – Must have Extubation attempted if all present for > 12 hours

- **> 48 hrs of age (24-25wk)**
- **FiO2 <.40 for SpO2 ≥ 90%**
- **pH > 7.30 or PaCO2 < 50 torr**
- **MAP < 8 cm H20 Rate < 15 bpm, If HiFi Amp < 2X MAP**
- **Hemodynamic stability**
- **No significant PDA**

COT Trial –Proph/Early Surf - Control 24-25 6/7ths and 26-27 6/7ths weeks

Must RE-intubate if

- $PaCO_2 > 55$ torr and
- $FiO_2 \geq .40$ for $SpO_2 < 90\%$

for > than 4 hours

Criteria apply for first 14 days of life for 24-25 weeks and 7 days for 26-27 weeks

Oxygen Saturation Monitoring Arm

Birth – Admit to NICU
Placed on Study PO

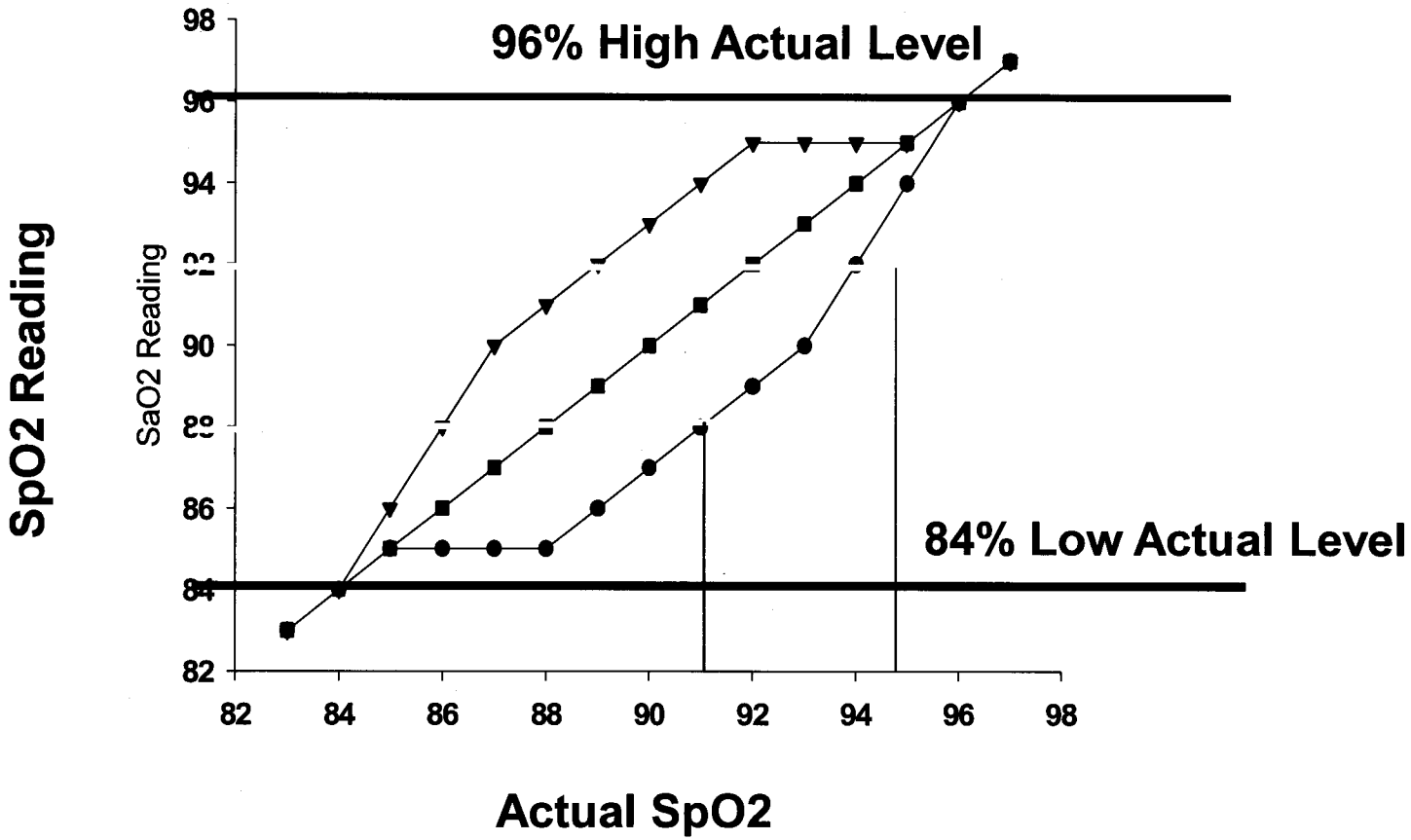
SpO2 Targets

SpO2 – 85% - 89% **SpO2 – 91% - 95%**

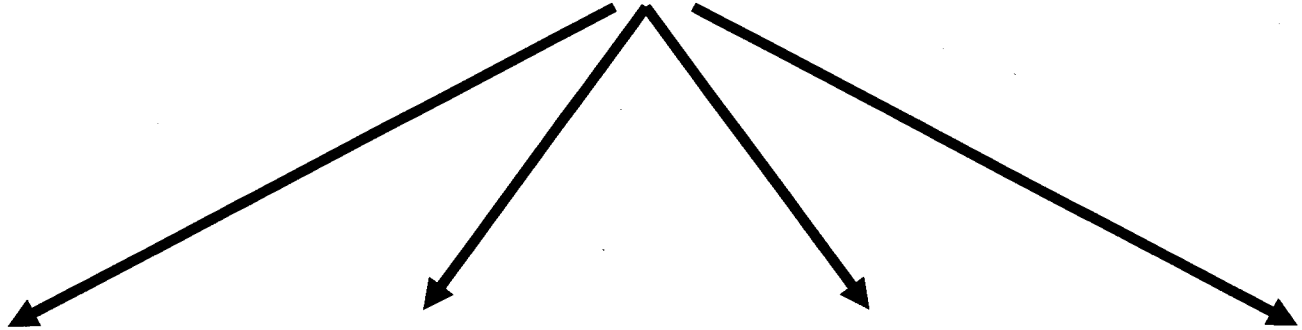
Maintain till off ventilatory support and Oxygen

	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO2 range group	88-92%	85-89%	85-95%	85-94%
High SpO2 range group	88-92%	91-95%	85-95%	86-95%

Plot of Actual versus Displayed SpO2



Overall Study Design



CPAP + Lo SpO2 CPAP + Hi SpO2 Surf + Hi SpO2 Surf + Lo SpO2

CPAP = Treatment Group

Surf = Control Group

Sample Size Estimate

- **The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.**

Occurrence of Death (D) and BPD, CLD and NDI for each Possible Study Subgroup

Subgroup D/NDI	D/BPD	D/> Stage III ROP
23-27 GA 65.7	70.6	53.1
24-28 GA 59.3	64.8	44.5
24-27 GA 60.7	66.6	46.8
23-28 GA 64.0	68.6	50.4

Sample Size

- We will use a 10% difference and a power of 80% for the outcomes of Death/BPD and Death/ROP
- We will randomize multiple pregnancies to same arm
- This will require an increase in sample size X 1.12

Sample Size

- This will require a sample size of 1310 infants
- Adding 15% attrition factor results in a total of 1506 infants.
- This will also provide an 80% power to evaluate Mortality/NDI.

COT Trial Review

- Protocol now simpler and identical for both arms apart from duration of criteria
- Comparison of Prophylactic/Early Surfactant vs CPAP
- Lower vs Higher SpO2 using ranges and design identical to POST ROP starting at 1 hour continued till off oxygen
- Pre-delivery consent and Randomization, by family

COT Trial - Issues

- Give Masimo go ahead to finalize prototype POs that will be tested at 5 Vent Centers to ensure ranges, averaging, and downloads as programmed - 3 -4 months
- Develop study manual – 3- 4 months
- Complete Benchmarking – earliest July
- Target initial enrollments for August-Sept

- Masimo can produce 200 devices within 1 month or less
- Consider need for site visits and/or develop video for in-service
- Each site to use study POs on at least 2-4 patients prior to site enrollment

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: DR CPAP
Date: Thursday, February 19, 2004 5:21:01 PM

Yes
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Sent: Thursday, February 19, 2004 12:11 PM
Subject: DR CPAP

Neil
Can we get a final protocol by mid-March for posting ont he web??
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: DRCPAP
Date: Thursday, February 26, 2004 2:22:03 PM
Attachments: DRCPAP pilot closeout 2004 A budget.xls

No sure what it takes to close out a study. But I reviewed the enrollment numbers for the DRCPAP and it looks like the sites "owe" us some money. See attached.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

FY2003 A DR CPAP DRAFT BUDGET per patient reconciliation

	Estimated # Pilot patients	Data collection (4hrs@$32/hr)	subtotal direct pilot	Indir Factor	Indirect Costs	Total Pt award	Actual # of Pts enrolled	Diff	Data collection (4hrs@$32/hr)	subtotal direct pilot	Indir Factor	Indirect Costs	Total Pt award	Reconciled FY 2003 Pil
Case*	20	$2,560	$2,560	0.53	$1,357	$3,917	11	(9)	$1,408	$1,408	0.53	$746	$2,154	($1,763)
Texas-Hstn														
Texas-Dls														
Wayne St														
Miami*	30	$3,840	$3,840	0.515	$1,978	$5,818	29	(1)	$3,712	$3,712	0.515	$1,912	$5,624	($194)
Emory														
Cincinnati*	25	$3,200	$3,200	0.53	$1,696	$4,896	12	(13)	$1,536	$1,536	0.53	$814	$2,350	($2,546)
Indiana														
Yale														
Brown														
Stanford														
Alabama*	35	$4,480	$4,480	0.435	$1,949	$6,429	32	(3)	$4,096	$4,096	0.435	$1,782	$5,878	($551)
WFU														
Duke														
Rochester														
								0						
UCSD*	40	$5,120	$5,120	0.515	$2,637	$7,757	20		$2,560	$2,560	0.515	$1,318	$3,878	($3,878)
Totals	150	**$19,200**	**$19,200**	**0.51**			**104**		**$13,312**	**$13,312**				**($8,932)**

FY2001- B DR CPAP DRAFT BUDGET															
	Estimated # Pilot patients	PILOT Start-up	Equipment	Supplies	Data collection (4hrs@$32/hr)	subtotal direct pilot	Start-up + training	TRIAL Estimated umber of total pts	Equipment	Supplies	*Ventilation* Data collection @$1000/pt	Total direct	Indir Factor	Indirect $$	2001-B TOTAL
Case*	20	2000	$5,000	$500	$2,560	$10,060	$2,000	33			$33,000	$43,060	0.53	$22,822	$65,882
Texas-Hstn							$2,000	40	$5,000	$500	$40,000	$45,500	0.495	$22,523	$68,023
Texas-Dls							$2,000	28	$5,000	$500	$28,000	$33,500	0.56	$18,760	$52,260
Wayne St							$2,000	33	$5,000	$500	$33,000	$38,500	0.49	$18,865	$57,365
Miami*	30	2000	$5,000	$500	$3,840	$11,340	$2,000	45			$45,000	$56,340	0.515	$29,015	$85,355
Emory							$2,000	28	$5,000	$500	$28,000	$33,500	0.28	$9,380	$42,880
Cincinnati*	25	2000	$5,000	$500	$3,200	$10,700	$2,000	40			$40,000	$50,700	0.53	$26,871	$77,571
Indiana							$2,000	40	$5,000	$500	$40,000	$45,500	0.49	$22,295	$67,795
Yale							$2,000	13	$5,000	$500	$13,000	$18,500	0.299	$5,532	$24,032
Brown							$2,000	33	$5,000	$500	$33,000	$38,500	0.393	$15,131	$53,631
Stanford							$2,000	18	$5,000	$500	$18,000	$23,500	0.6	$14,100	$37,600
Alabama*	35	2000	$5,000	$500	$4,480	$11,980	$2,000	50			$50,000	$61,980	0.435	$26,961	$88,941
WFU							$2,000	48	$5,000	$500	$48,000	$53,500	0.45	$24,075	$77,575
Duke							$2,000	33	$5,000	$500	$33,000	$38,500	0.54	$20,790	$59,290
Rochester							$2,000	28	$5,000	$500	$28,000	$33,500	0.595	$19,933	$53,433
UCSD*	40	2000		$500	$5,120	$7,620	$2,000	50			$50,000	$57,620	0.515	$29,674	$87,294
Totals	150		**$20,000**	**$2,500**	**$19,200**	**$51,700**	**$32,000**	560	**$55,000**	**$5,500**		**$672,200**		**$326,726**	**$998,926**

*Pilot enters; funds for all other centers restricted

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DRCPAP
Date: Thursday, February 26, 2004 2:41:29 PM

Ok, I am just revisiting all the budgets so when we hit early March we can crank these out. Thanks for verifying.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 26, 2004 2:33 PM
To: 'Petrie, Carolyn'
Subject: RE: DRCPAP

This is correct, the sites owe us money and they have more allocated. We can rectify this once I get final word on potential co-funding for this project.
Thanks
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, February 26, 2004 2:22 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: DRCPAP

No sure what it takes to close out a study. But I reviewed the enrollment numbers for the DRCPAP and it looks like the sites "owe" us some money. See attached.

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD)
Subject:	FW: Neonatal Research Network COT TRIAL
Date:	Friday, February 27, 2004 2:04:46 PM
Attachments:	COT Study October 31 2003.doc

Attached is the email sent to the DSMC regarding the DRCPAP trial.
carolyn

-----Original Message-----
From: Petrie, Carolyn
Sent: Friday, October 31, 2003 3:21 PM
To: George Rhoads MD (rhoads@rwja.umdnj.edu); John Sinclair MD (sinclair@mcmaster.ca); Larry Gilstrap MD (Larry.C.Gilstrap@uth.tmc.edu); M. D. Alan Jobe (Jobea0@chmcc.org); Mark Klebanoff MD (mk90h@nih.gov); Roberta Ballard MD (ballard@email.chop.edu); Carol Redmond Ph. D. (ckr3+@pitt.edu); John C. Fletcher Ph. D. (jcf4x@unix.mail.virginia.edu); M. D. Christine A. Gleason (cgleason@u.washington.edu); M. D. Gordon Avery (gavery@cnmc.org); M. D. Mary D'Alton (md511@columbia.edu)
Cc: Hastings, Betty J.; Petrie, Carolyn; 'aRose Higgins (higginsr@mail.nih.gov)'; Poole, W. Kenneth
Subject: Neonatal Research Network COT TRIAL

Good Afternoon!

The attached study, "Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants" was approved by the Neonatal Research Network.

Please review and send me your comments by **Friday November 21**.

Thank you,
Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 420
Rockville, MD 20852
ph. (301) 230-4648
fx. (301) 230-4646

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: delivery room CPAP/ oxygen saturation trial
Date: Friday, February 27, 2004 4:21:17 PM

Vivek Narendran will be the site PI for this study in Cincinnati. Vivek is responsible for managing our early CPAP program and he did publish an observational study in J. Perinatology on this topic. Both Kurt Schibler and I will be helping him.

Edward F. Donovan, M.D.
Director
Child Policy Research Center
Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 02/27/2004 3:24:47 PM >>>
Hi,
I have received a few requests to have "site PI's" for the upcoming DR CPAP trial. I believe this is an excellent idea and if PI's would like another neonatologist at their site to be the PI for this project let me know.

In addition, it is highly likely that we will receive co-funding for this project from National Heart Lung and Blood Institute for which I am extremely grateful.

Have a good weekend!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From:	Neil Finer
To:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Fw: COT Trial Jan 20 04
Date:	Tuesday, January 20, 2004 7:47:30 PM
Attachments:	COT Trial Jan 20 04.doc Summary- External Reviews and responses Jan 04.doc

---

Rose
Hearing no objections, you may send out these documents to the Steering Committee. I hope that these do not encourage another need for further reviews.
See you next week
Neil
----- Original Message -----
From: Neil Finer
To: Neil Finer ; Wally Carlo, M.D. ; Shahnaz Duara ; Donovan, Edward (DONOVAEF) ; Avroy A. Fanaroff, M.D. ; Rosemary Higgins
Sent: Sunday, January 18, 2004 9:02 PM
Subject: COT Trial Jan 20 04

Hello Everyone
Rose has asked that we send out the revision to the PIs. I have made a very few revisions, and left the infants < 500gm and used a PaCO2 of 50 for extubation of controls with a pH > 7.30.
I have also attached my brief response to the critiques. I would prefer that the protocol be our response to these.
Please review and send me and Rose an e-mail to indicate if we should send out a response to the critiques, or just send the external reviews and the current protocol.
We should get these to the PIs by Wednesday if possible
See you next week
Be well
Neil

Protocol for the NICHD Neonatal Research Network

Continous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

Jan 20, 2004

Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

1.1 Statement of Problem

At the present time, there is no recommendation or standard teaching regarding the early use of CPAP/PEEP during resuscitation and continuing after NICU admission for the extremely low birth weight (ELBW) infant. However, a number of studies, mostly retrospective in nature, have suggested that the use of early CPAP may be associated with improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in oxygen supplementation and/or death at 28 days after birth and at 36 weeks post menstrual age. There has not been a prospective study which has randomized ELBW infants to CPAP/PEEP beginning in the delivery room, and continuing in the NICU and a permissive ventilation strategy if intubation is required and compared their outcomes to infants treated with prophylactic or early natural surfactant, interventions with known efficacy in reducing mortality, severity of disease and the incidence of chronic lung disease (CLD).

Retinopathy of prematurity (ROP) remains a significant cause of morbidity among ELBW infants, and its occurrence is inversely proportional to gestational age and duration of oxygen exposure. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, and but early trials were unable to pinpoint the actual level of arterial PaO_2 which was the threshold for triggering the pathophysiology of this disorder.[1] However, there have been a very few prospective studies evaluating the benefit of higher versus lower levels of oxygenation in infants, especially for ELBW infants, none of which were performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges, and adherence to strict nursery policies may result in a lower incidence of severe ROP, there is no current agreement on the accepted SpO2 ranges for managing the ELBW infant from birth.

1.2 Background

Positive End Expiratory Pressure (PEEP) has been shown to be of benefit in maintaining functional residual capacity (FRC). Although no formal recommendation has been made to date about maintaining PEEP in the delivery room setting, continuous positive airway pressure appears beneficial during cardiopulmonary resuscitation[2]. Gregory et al in 1971 first demonstrated that the use of CPAP started at approximately 5.9hours ($\pm$12.4hrs) for their infants < 1500 gm at birth, improved oxygenation[3] in newborn infants with respiratory distress; these observations were followed by prospective studies that demonstrated improved survival in premature infants treated with early CPAP[4]. Premature infants who do not achieve a FRC are more likely to develop hyaline membrane disease (HMD) requiring mechanical ventilation[5]. CPAP may prevent the excessive consumption of surfactant in newborn infants with limited surfactant production.[6] A review of prospective studies evaluating early (not delivery room) CPAP in the pre-surfactant, pre-antenatal steroid era suggested that early CPAP may improve survival in infants greater than 1500 gm.[7]

Similarly, there is no definite recommendation or standard teaching regarding the level of oxygenation that should be maintained in ELBW infants. Oxygen supplementation has to be used liberally as ELBW infants frequently have desaturation episodes and thus wide saturation ranges are tolerated clinically. However, oxygen toxicity can result in increased risk for CLD, retinopathy of prematurity (ROP) and other disorders. Alternatively, oxygen restriction may impair neurodevelopment. The pulse oximeter is a newer technology that can be used to

improve the control of oxygenation levels. There is great potential benefit to determining the oxygenation levels that prevents ROP and CLD but does not result in neurodevelopmental impairment with a randomized controlled trial of levels of oxygen saturations on the high and low side of the currently utilized levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels may result in an increase in periods of hypoxemia because of the marked variability in oxygen in ELBW infants. Thus, it is necessary to determine if lower oxygenation levels that may prevent ROP and CLD are deleterious for brain development and result in impaired neurologic outcome.

.

1.3 Animal Studies

Nilsson et al demonstrated that the use of 5 cm H_2O PEEP in the initial ventilation of premature rabbit pups resulted in increased lung-thorax compliance, and reduced the extent of bronchiolar epithelial lesions seen with mechanical ventilation [8]. The use of early PEEP starting at delivery, improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [9,10]

More recently studies by Jobe et al have demonstrated that premature lambs treated with CPAP alone at birth had significantly decreased neutrophils and hydrogen peroxide in their alveolar wash when compared with animals who were ventilated from birth.[11]

1.4 Human Experience: Ventilatory Support

CPAP was introduced by Gregory et al in 1970 and was shown to improve gas exchange and outcomes in preterm infants with respiratory distress.[12] A subsequent review of CPAP for respiratory distress concluded that "In preterm infants with RDS the application of CDP either as CPAP or CNP is associated with benefits in terms of reduced respiratory failure and reduced mortality. CDP is associated with an increased rate of pneumothorax. The applicability of these results to current practice is difficult to assess, given the intensive care setting of the 1970s when four out of five of these trials were done."[13]

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality (p=0.038), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those $\geq$1000 g (P <0.02 and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; p < .05, and the proportion of infants ≥1000 g in whom BPD developed decreased from 14% to 9%; p < .05. None of these observations was from a

prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.[17] No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."[18]

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.[19] The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. 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 COT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 25 6/7ths weeks with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes. We will compare prophylactic surfactant with DR CPAP in the 26 to 27 6/7ths weeks infants.

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.

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.[51] 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[52] using a 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.

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 ($\leq$ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

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%**

Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control Prophylactic Surfactant	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic 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 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 completed weeks (up to 27 6/7th) who weigh 500 gm or more 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
- 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 $\geq$ 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 at risk for premature delivery at 276/7ths 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.

3.6 Other Procedures

Neopuff resuscitators, equivalent T-piece resuscitators or a Neonatal ventilator including disposable circuits, will be provided to all sites for delivery room management. Sites may use equivalent devices that are already available. A training video to explain the proper use of the Neopuff® will be provided to each site in advance of a site visit.

3.7 Randomization

Gestation-specific, stratified. Randomization will occur prior to delivery and will be performed by utilizing specially prepared double-sealed envelopes. Each randomization will indicate randomization to either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic surfactant and conventional ventilator management) and to 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 would reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants management, and allowing 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.

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 surfactant whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The intervention to either a high or low SpO2 by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 1 hour following NICU admission.

For infants in the 24 0/7ths to 25 6/7ths weeks gestation, the infant will be weighed on admission to the NICU. They will be randomized prior to delivery, and their DR management will follow protocol. If they weigh less than 500gm they will be excluded from the trial, and not randomized to a study pulse oximeter. There will be a delivery room data form to be completed for these infants.

TREATMENT Group : Early Extubation and CPAP
Protocol:

Treatment Group – Delivery Room Management: 24 – 25 weeks Stratum (≥ 500 gm birth weight). Infants will be stabilized and then placed on CPAP in the delivery room. They will be weighed on admission to the NICU.

Treatment Infants - NICU Management: 24 - 25 weeks

All Treatment infants of 24-25 wks stratum who are intubated for resuscitation will be given surfactant. They will then be extubated by 1 hour of age, if they meet the Criteria for Extubation, as outlined below. All Treated infants will managed with a permissive ventilation strategy which will involves the acceptance of higher PaCO2s and will require an FiO2 > 50% before intervention. (Over 90% of Infants of 24-25 weeks gestation in the Network are currently intubated and ventilated for a mean of > 20 days.)

Extubation Criteria for Intubated Treatment Infants of 24 to 25 weeks at 1 hour

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An indicated SpO2 ≥ 90% with an FiO2 ≤ 50%
- Hemodynamically stable defined as a stable blood pressure for age, with evidence of adequate perfusion in the absence of the need for pressor or volume support.

All Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow (if available) or comparable apparatus, with the CPAP being initiated at 5 cm H20. The level of CPAP may be increased to up to 8 cm to maintain acceptable SpO2. Nasal SIMV may be used to treat infants post-extubation to treat clinical apnea or elevated PaCO2 in bothTreatment or Control Infants.

Subsequent Intubation Criteria for Treatment infants

Treatment Infants will be intubated ***if any of the following criteria are met:***

- $PaCO_2$ > 65 torr with a pH < 7.20 (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An indicated SpO2 ≥ 90% with an FiO2 ≥ 50%
- Hemodynamic instability defined as a blood pressure less than gestational age for the first 24 hours, and subsequently below expected norms (will be provided) unresponsive to volume and/or pharmacologic support.

These criteria will continue in effect for 14 days from birth. (The average duration of ventilation of such infants is > 21 days for all centers)

Extubation Criteria for Intubated Infants in Treatment Group: 24 – 25 weeks stratum

An intubated Treatment infant either not able to be extubated at 1 hour, or reintubated ***MUST have extubation attempted within 24 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An indicated SpO2 ≥ 90% with an FiO2 ≤ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (blood pressure normal for age, not on pressor support)

These criteria will continue in effect for 14 days from birth. (The average duration of ventilation of such infants is > 21 days for all centers)

Re-Intubation of an Extubated Treatment Infant:

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 up to 48 hrs based on the clinician's decision.

Delivery Room Management : Treatment Group – 26 0/7ths-27 6/7ths weeks Stratum - Infants will be resuscitated using whatever FiO_2 represents current practice in each unit and CPAP or positive pressure ventilation with PEEP (if the infant requires positive pressure ventilation, PPV) until admission to the NICU using the Neopuff or equivalent device and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O. The Neopuff® or equivalent (See Section **3.6**) will be used to deliver initial CPAP in the delivery room for infants randomized to the Early CPAP group, and may be used for resuscitation of the conventional group.

It is acceptable to insert nasal prongs in the delivery room and transport on such a device with CPAP or PPV/PEEP to the NICU.

Infants will be resuscitated using whatever FiO2 represents current practice in each unit and CPAP or positive pressure ventilation with PEEP until admission to the NICU using the Neopuff or equivalent device and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H2O and a PEEP/CPAP of 5 cm cmH2O.

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice, apart from the restriction that treatment infants may not be intubated for sole purpose of giving surfactant in the delivery room (DR).

Infants who require intubation for resuscitation in the Treatment group will receive surfactant in the DR area at the discretion of the attending physician, or once in the NICU, with the recommendation that such surfactant be given within 30 $\pm$15 minutes of birth for Treatment infants who required DR intubation.

Thus earlier intubation in the Treatment Group 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. This was the approach used for the DR CPAP feasibility trial.

NICU Management -Treatment Infants: 26 - 27 weeks Stratum

These infants will be managed on nasal CPAP, or Nasal SIMV and may be intubated if they meet any of the criteria listed below. If intubated within the first 72 hours of life they should receive surfactant

Criteria for Initial Intubation or Re-intubation for Treatment infants of 26-27 weeks not intubated in DR:

Infants meeting the ANY of these criteria MUST be intubated and given surfactant (within the first 48 hours of life)

- An FiO_2 >.50 to maintain an indicated SpO2 $\geq$ 90% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) for 2 successive blood gases at least 15 minutes apart.
- Hemodynamic instability defined as a low blood pressure for age and/or poor

perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for 7 days from birth. (The average duration of ventilation of such infants is 6 days for all centers with a range of 2.8 to 8.1 days)

Treated infants of 26 – 27 wks who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be restarted at any time in such infants.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Repeat Surfactant administration may be given to Treatment infants if the FiO2 is greater than 50% following manufacturers' recommendations for dose, and dosing interval, up to 4 doses.

Re-Intubation of an Extubated Treatment Infant:

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.

Extubation Criteria for Intubated Infants in Treatment Group: 26 – 27 weeks stratum

An intubated Treatment infant ***MUST have extubation attempted within 24 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\geq$ 90% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable

These criteria will continue in effect for 7 days from birth. (The average duration of ventilation of such infants is 6 days for all centers with a range of 2.8 to 8.1 days)

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 these 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 Group: Prophylactic Surfactant and Ventilation

Overview:

Control infants are to be treated using an approach considered similar to current standards of care. The requirements for intubation of such infants are based on the best evidence to date suggesting that prophylactic surfactant by 15 minutes or early surfactant within 2 hours of birth provide a significant survival benefit. This approach will be used for all infants in the all Control Infants in both strata.

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.

Control Infant Protocol

Control Group – Delivery Room Management : 24 – 25 weeks Stratum, > 500 gm birth weight. Infants will be intubated in the delivery room and given surfactant or receive surfactant within 30 ±15 minutes of birth. They will be weighed on admission to the NICU.

Control Group - NICU Management: 24 – 25 weeks strata

Infants will continue to receive mechanical ventilation until extubation criteria are satisfied with a minimum duration of ventilation of 48 hours

Extubation Criteria for Intubated Control Group infants: 24 – 25 weeks strata

Extubation ***MUST*** be attempted if ***ALL*** of the following criteria are present

- Infant is > 48 hours of age
- $PaCO_2$ < 50 torr and pH > 7.30(arterial or capillary samples)
- An FiO2 < .40 with a SpO2 > 90% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- 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 from birth.

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.

Extubation of Control infants who do not meet any of these criteria will be recorded as a study violation.

Re-intubation Criteria of Extubated Control Infants:

Control Infants meeting *Both* of these criteria for more than 4 hours *MUST* be intubated, and *MAY* be intubated for less severe criteria

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- An FiO2 > .40 with or without CPAP to maintain an SpO2 < 90% for a minimum of 30 minutes using the study pulse oximeters.

These criteria will continue in effect for a minimum of 14 days from birth.

(Note: A Control infant who meets both criteria during the first 14 days of life MUST be intubated.)

Control Group – Delivery Room Management : 26 – 27 weeks Stratum: Infants can be intubated in delivery room and given surfactant within 30 + 15 minutes of birth, but **MUST** be intubated and receive surfactant if they meet the criteria listed below by the first hour of life.

Control Group - NICU Management: 26 – 27 weeks strata

The infants in this stratum who where not intubated in the DR, will be evaluated for intubation and surfactant, and all other infants in this stratum will continue to receive mechanical ventilation until extubation criteria are satisfied.

Control infants of 26 to 27 weeks who were not intubated at delivery MUST be intubated if they meet ANY of these criteria within the first hour of life and given surfactant.

- An FiO_2 >0.3 to maintain an indicated SpO2 ≥ 90% with or without CPAP using study oximeter
- A $PaCO_2$ > 55 torr

Repeat surfactant administration may be given if the FiO2 is > 40%

A review of the Network data for 2002 revealed that 82% of infants from 26-27 weeks were intubated for surfactant, with a range from 56% to 100% in individual centers. Thus this protocol may result in either an increase or decrease in the intubation of control infants compared to the current Network experience.

The Current Protocol essentially forces the use of prophylactic surfactant for all Control infants, but allows the surfactant to be delayed till one hour in recognition of the practice patterns at some Network units.

The protocol will require that all eligible infants in this stratum are intubated and receive prophylactic/early surfactant.

Extubation Criteria for Intubated Control Group infants: 26 – 27 weeks strata

Extubation ***MUST*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 50 torr (arterial or capillary samples) with a pH > 7.30
- An FiO2 < .40 with a SpO2 > 90% 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)

These criteria will continue in effect for a minimum of 14 days from birth.

There is not a specified weaning protocol, so that we are leaving significant room for the individual clinicians to get to these settings.

Re-intubation for Control Infants 26 – 27 weeks:

Non-intubated Control Infants meeting all of these criteria for more than 4 hours *MUST* be intubated.

- $PaCO_2$ > 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- pH < 7.25

- An FiO2 > .40 with or without CPAP with a SpO2 < 90% using the study pulse oximeters

These criteria will continue in effect for the first 14 days from birth.

Any unplanned, accidental extubation of a control infant does not require immediate re-intubation, and such infants may be treated with CPAP, but if infant meets re-intubation criteria within the first 14 days of life for more than 4 hours, intubation should be performed.

Following planned extubation, CPAP or NSIMV may be used for Control infants, but the above criteria for re-intubation will be in effect until 14 days of life, apart from the use of CPAP/NSIMV and an FiO2 > 0.50.

For all Infants, Both Strata

For any infant in any arm of this trial, 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. All the above criteria will be in effect for the first 14 days of life, following which current unit practice will dictate management.

Repeat surfactant dosing should follow the manufacturers' recommendations for dose and interval, and criteria are indicated in the protocol. Repeat dosing is not required by the study protocol.

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) 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 94%. 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 gradually 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 following NICU admission, with a

maximal allowable delay of 60 minutes. 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 discharge, or retinal maturity, or in the absence of ROP, 36 weeks PCA whichever is later.

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, or retinal maturity, or in the absence of ROP 36 weeks PCA whichever is later.

These interventions will be delivered using specially developed pulse oximeters whose CRT outputs (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%. 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 85% to 95% for both groups. 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 CRT output will be the same in both groups (Table).

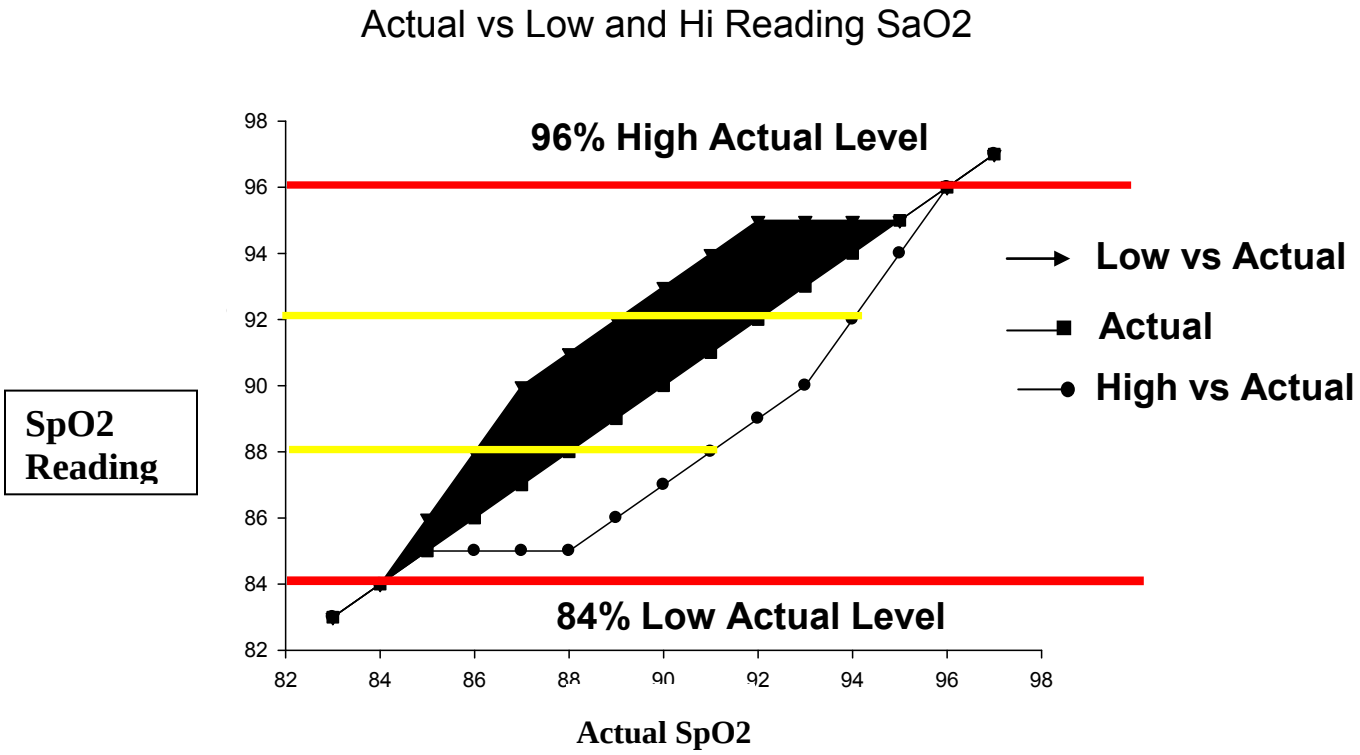
Table. Output and Actual SpO2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SpO2 range group	88-92%	85-89%	85-95%	85-94%
High SpO2 range group	88-92%	91-95%	85-95%	86-95 %

In addition, and as an added safety issue, we will be asking the pulse oximeter provider to program the software of the actual pulse oximeters used in this trial to return to the actual reading when then the actual 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, ie < 85% and hyperoxia, ie SpO2 > 95%. An infant with an SpO2 outside these limits will have his/her actual SpO2 displayed on their pulse oximeter available for their caretakers to allow appropriate intervention. We have asked the manufacturer to utilize the averaging algorithm of 16 seconds in keeping with current clinical practice. Some network centers use an averaging interval of 30 seconds. This averaging time will permit the change in reading from the altered readings to the actual SpO2 values without unmasking the caretakers.

We believe that this methodology will reassure all caretakers, and provide an acceptable ethical design for this trial. In addition we are confident that caretakers will not be aware of the shift from altered SpO2s to actual values, as few if any caretakers actually watch the changes in SpO2 but are alerted to do so by alarms. Thus in most circumstances by the time the caretaker responds to an alarm, the change from altered to actual SpO2 will have, in most circumstances,

already occurred. 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 96% which will ensure that the infants SpO2 will be separated throughout this range.



At 3 days and every subsequent 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per each second of monitoring for a 72 hour period), from the study pulse oximeters will be downloaded and transmitted without further review or analyses 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 28 days 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 and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a device called a “NeoPuff®” or an equivalent device (See **3.6**). This device is pressure driven and operator cycled using an occlusion valve at the patient T-piece to allow the resuscitator to set both the Peak Inspiratory Pressure (PIP) and the PEEP or CPAP level, and to control the rate of ventilation. This device can also deliver CPAP

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.[535455]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants.

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[56]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

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 (**See Section 4.1**)
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:

1. Air leak on admission to the NICU
2. The need for chest compressions, and/or epinephrine in the delivery room
3. The occurrence of severe IVH (Grades 3-4, Papile)[57]
4. Death

4.5 Resuscitation Associated Events

Resuscitation associated events will be noted and may include:
1. Significant bradycardia secondary to trigeminal stimulation
2. Significant gastric distension thought to be secondary to excessive airway pressure

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, ROP
- 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

6.1 Training Study Personnel

A training video on the use of the Neopuff or equivalent device, and the set-up and use of the video recording apparatus will be distributed to sites for review before the training site visit. The site visit by the PI and representatives from Fisher-Paykel (distributors of Neopuff) to install the equipment and in-service the Neopuff and the Bubbleflow for CPAP if available. Training will be provided as well as a detailed protocol for obtaining and transmitting the stored PO SpO2 and Heart rate data.

6.1.1 Job Descriptions of Study Personnel

The NICHD Coordinators will assist the Respiratory therapists in each unit regarding the set up the Neopuff equipment and bubbleflow apparatus (if utilized for CPAP – currently not FDA approved).

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during a dedicated training meeting. In addition the study staff will have extensive in-service regarding the study POs utilized.

6.1.3 Training Materials and Certification

A training video to review the set-up of the Neopuff, and the bubbleflow will be distributed and sites will be certified on the use of the Neopuff, and bubbleflow apparatus.

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 Chi square 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). The primary analysis will determine if there is an interaction 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 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 first two 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% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and the lower of the two outcome rates, 65%, 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%	1600	1872	2040	2388
9%	1240	1450	1600	1872
10%	1000	1170	1300	1522
11%	840	984	1080	1264
12%	700	820	920	1076
13%	600	702	768	900
14%	520	608	672	786
15%	448	524	584	684

These sample sizes are not sufficient to permit detection of interactive effects between the two treatments with reasonable power. We will use a 10% difference, and project a sample size of 1170 infants, adding 15% attrition factor for a total of 1345 infants. This will provide an 80% power to evaluate Mortality/NDI.

HYPOTHESIZED TREATMENT EFFECTS FOR COT

When sample sizes were estimated for the COT trial the following base rates for the three outcomes 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 DRCPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
DRCPAP	Yes	45	55	50
	No	55	65	60
Overall		50	60	55

Table IB

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on BPD/Mortality **Assuming a 10% Main Effect for DRCPAP Only**—Table Entries are Outcome Rates (%)

		SpO2		
		Low	High	Overall
DRCPAP	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

		Low	High	Overall
DRCPAP	Yes	25	35	30
	No	35	45	40
Overall		30	40	35

Table IIB

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on ROP≥ Grade III/Mortality **Assuming a 10% Main Effect for SpO2 Only**—Table Entries are Outcome Rates (%)

SpO2

		Low	High	Overall
DRCPAP	Yes	35	45	40
	No	35	45	40
Overall		35	45	40

Table III

Treatment Effects for SpO2 (High, Low) and DRCPAP (Yes, No) on NDI/Mortality **Assuming a 10% Main Effect for Each Factor**—Table Entries are Outcome Rates (%)

SpO2

		Low	High	Overall
DRCPAP	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. On site monitoring will be performed by an initial site

visit, review of the data forms, and independent review of the video recordings, which contain the entire randomized elements of this study. Protocol violations will be reviewed, and if frequent, will 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 7-8cmH_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 infants 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				

Bibliography

1 Kinsey VE; Arnold HJ; Kalina RE, and et al. PaO2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics. 1977;60

2 Hevesi ZG, Thrush DN, Downs JB, Smith RA. Cardiopulmonary resuscitation - Effect of CPAP on gas exchange during chest compressions. Anesthesiol 1999;90(4):1078-1083.

3 Gregory GA, Kitterman JA, Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. New Engl J Med 1971;284:1333-40.

4 Rhodes P, Hall RT. CPAP delivered by face mask in infants with the idiopathic respiratory distress syndrome: A controlled study. Pediatr 1973;52:17-21

5 Upton CJ, Milner AD. Endotracheal resuscitation of neonates using a rebreathing bag Arch Dis Child 1991;66:39-42

6 Bos J, Lachmann B. Surfactant function: is it influenced by artificial ventilation? In: Cosmi EV, ed. The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome. London, England: MacMillan Press; 1991:96-106

7 Ho, JJ, Subramanian, P, Henderson-Smart, DJ, Davis, PG. Continuous distending pressure for respiratory distress syndrome in preterm infants. The Cochrane library, Issue#3, 2002, Update Software

8 Nilsson, R. The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. Acta. 1982 Apr; 26(2):89-103.

9 Hartog, A.; Gommers, D.; Haitsma, J. J., and Lachmann, B. Improvement of lung mechanics by exogenous surfactant: effect of prior application of high positive end-expiratory pressure. British Journal of Anaesthesia. 2000; 85(5):752-756

10 Michna, J.; Jobe, A. H., and Ikegami, M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. American Journal of Respiratory and Critical Care Medicine. 1999; 160(2):634-639

11 Jobe, A. H.; Kramer, B. W.; Moss, T. J.; Newnham, J. P., and Ikegami, M. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. Pediatric Research. 2002; 52(3):387-392

12 Gregory GA; Kitterman JA; Phibbs RH, et al. Treatment of the idiopathic respiratory distress syndrome with CPAP. NEJM. 1971; 284,

13 Ho JJ, Subramaniam P, Henderson-Smart DJ, Davis PG Continuous distending pressure for respiratory distress syndrome in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

14 Jonsson B, Katz-Salamon M, Faxelius G, et al. Neonatal care of very-low-birthweight infants in special-care units and Neonatal intensive-care units in Stockholm. Early nasal continuous positive airway pressure versus mechanical ventilation; gains and losses. Acta Pediatr Suppl 1997;419:4-10.

15 Gittermann MK, Fusch C, Gittermann AR, et al. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birthweight infants. Eur J Pediatr 1997;156:384-8

16 Poets, C. F. and Sens, B. Changes in intubation rates and outcome of very low birth weight infants: A population-based study. Pediatrics. 1996 Jul; 98(1):24-27

17 Han VKM, Beverley, DW, Clarson C, et al. Randomized controlled trial of very early continuous distending pressure in the management of preterm infants. Early Human Development1987;15:21-32

18 Subramaniam P, Henderson-Smart DJ, Davis PG Prophylactic nasal continuous positive airways pressure for preventing morbidity and mortality in very preterm infants (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

19 Verder, H.; Robertson, B.; Greisen, G.; Ebbesen, F.; et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. New England Journal of Medicine. 1994 Oct 20; 331(16):1051-1055

20 Verder H, Albertsen P, Ebbesen F, Greisens G, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics 1999;103(2):E241-E246.

21 Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birthweight infants: Spontaneous breathing or intubation? Pediatrics 1999;103(5):961-7.

22 Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987;79:26-30.

23 Van Marter LJ, Allred EN, Pagano M, et al. Do clinical markers of barotrauma and oxygen toxicity explain inter-hospital variation in rates of chronic lung disease? Pediatrics 2000;105(6):1194-201.

24 de Klerk AM, de Klerk RK. Nasal continuous positive airway pressure and outcomes in preterm infants. J Paediatr Child Health 2001;37:161.

25 Sandri, F, Ancora G, Mosca F, et al. Prophylactic vs rescue nasal continuous positive airway pressure in preterm infants: Preliminary results of a multicenter randomized controlled trial. Pediatr Res 2001;49:273A.

26 Thomson M, on behalf of the IFDAS study group. Early Nasal Continuous Positive Airway Pressure with Prophylactic Surfactant in Infants at Risk for RDS. The IFDAS Multi-Centre Randomized Trial. Pediatr Research 2002, 45:321A

27 Kattwinkel J, ed. The Textbook of Neonatal Resuscitation. Fourth Edition: American Academy of Pediatrics and. American Heart Association, 2000.

28 Pandit, Paresh; Courtney, Sherry; Pyon, Kee, and et al. Work of breathing during constant- and variable-flow nasal continous positive airway pressure in preterm neonates. Pediatrics. 2001 Sep; 108(3):682-685.

29 Courtney, Sherry; Pyon, Kee; Saslow, Judy, and et al. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of three devices. Pediatr . 2001 Feb; 107(2):304-8.

30 Stefanescu, B. M.; Murphy, W. P.; Hansell, B. J.; Fuloria, M.; Morgan, T. M., and Aschner, J. L. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031-1038

31 Soll, RF. Prophylactic administration of natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review) in: The Cochrane Library. Issue 3, 2002, Update Software.

32 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software

33 Horbar JD, Bracken M, Buzas, J, Carpenter J, Leviton LL, Plesk, PE et al. Cluster randomized trial of a multifaceted intervention to promote evidence-based surfactant therapy. Pediatr Res 2003;53:368A

34 Tooley, J. and Dyke, M. Randomized study of nasal continuous positive airway pressure in the preterm infant with respiratory distress syndrome. Acta Paediatrica. 2003; 92(10):1170-1174

35 Silvers, K. M.; Gibson, A. T.; Russell, J. M., and Powers, H. J. Antioxidant activity, packed cell transfusions, and outcome in premature infants. Archives of Disease in Childhood. 1998; 78(3):F214-F219;

36 Saugstad, O. D. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica. 1997; 86(12):1277-1282

37 Luo, X. P.; Jankov, R. P.; Ning, Q.; Liao, L. J., and Tanswell, A. K. Oxygen-mediated parenchymal and vascular lung injury. Acta Pharmacologica Sinica. 2002; 2322-28

38 Davis, J. M. Role of oxidant injury in the pathogenesis of neonatal lung disease. Acta Paediatrica. 2002; 9123-25

39 Rozycki, H. J.; Comber, P. G., and Huff, T. F. (Rozycki HJ/Div Neonatal Perinatal Med/Box 980276/MCV Stn/Richmond,VA 23298 USA). Cytokines and oxygen radicals after hyperoxia in preterm and term alveolar macrophages. American Journal of Physiology Lung Cellular and Molecular Physiology. 2002; 282(6):L1222-L1228

40 Varsila, E.; Pesonen, E., and Andersson, S. (E Varsila/Helsinki Univ/Childrens Hosp/Helsinki, Finland). Early protein oxidation in the neonatal lung is related to development of chronic lung disease. Acta Paediatrica. 1995 Nov; 84(11):1296-129

41 Ramji, S.; Ahuja, S.; Thirupuram, S.; Rootwelt, T.; Rooth, G., and Saugstad, O. D. Resuscitation of Asphyxic Newborn Infants with Room Air or 100% Oxygen. Pediatric Research. 1993 Dec; 34(6):809-812

42 Saugstad, O. D.; Rootwelt, T., and Aalen, O. Resuscitation of asphyxiated newborn infants with room air or oxygen: An international controlled trial: The Resair 2 study. Pediatrics. 1998; 102(1):E11-E17

43 Vento, M.; Asensi, M.; Sastre, J.; GarciaSala, F.; Pallardo, F. V., and Vina, J. Resuscitation with room air instead of 100% oxygen prevents oxidative stress in moderately asphyxiated term neonates. Pediatrics. 2001; 107(4):642-647

44 Saugstad OD, Ramji S, Vento, M. Neonatal mortality is lower in depressed newly born infants if resuscitation is performed with ambient air instead of pure oxygen. A meta-analysis. Pediatr Res 53:376A, 2003

45 Lundstrom, K. E.; Pryds, O., and Greisen, G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. Archives of Disease in Childhood. 1995 Sep; 73(2 Sp. Iss.):F81-F86

46 Tin, W.; Milligan, D. W.; Pennefather, P., and Hey, E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001 Mar; 84(2):F106-10.

47 Bancalari E; Flynn J; Goldberg RN; Bawol R; Cassady J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics. 1987;79:663-669

48 Phelps, D. L.; Lindblad, A.; Bradford, J. D.; Wood, N. E.; Oden, N. L.; Cole, C et al, Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000; 105(2):295-310

49 Chow, L. C.; Wright, K. W., and Sola, A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003; 111(2):339-345

50 Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003; 349 (10): 953-961

51 Weinberger, B.; Laskin, D. L.; Heck, D. E., and Laskin, J. D. (Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology. 2002; 181(1):60-67

52 Finer NN, Rich W, Craft A, Henderson C, Comparison of methods of bag and mask ventilation for neonatal resuscitation. Resuscit 2001;49:299-305.

53 Barrington, K. J.; Bull, D., and Finer, N. N Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001; 107(4):638-641

54 Friedlich P; Lecart C; Posen R; Ramicone E; Chan L, Ramanathan R - A randomized trial of nasopharyngeal-synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. - J Perinatol 1999 Sep;19(6 Pt 1):413-8 .

55 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

56 Henderson-Smart DJ, Davis PG Prophylactic methylxanthines for extubation in preterm infants (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

57 Papile LA; Burstein J; Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birthweights less than 1500 grams. J Pediatr 1978;92:529-34

From:	Neil Finer
To:	Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Donovan, Edward (DONOVAEF); Avroy A. Fanaroff, M.D.; Higgins, Rosemary (NIH/NICHD)
Subject:	COT Trial Jan 20 04
Date:	Monday, January 19, 2004 12:04:18 AM
Attachments:	COT Trial Jan 20 04.doc Summary- External Reviews and responses Jan 04.doc

---

Hello Everyone
Rose has asked that we send out the revision to the PIs. I have made a very few revisions, and left the infants < 500gm and used a PaCO2 of 50 for extubation of controls with a pH > 7.30.
I have also attached my brief response to the critiques. I would prefer that the protocol be our response to these.
Please review and send me and Rose an e-mail to indicate if we should send out a response to the critiques, or just send the external reviews and the current protocol.
We should get these to the PIs by Wednesday if possible
See you next week
Be well
Neil

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT Study PI, RT, Coord
Date: Friday, May 14, 2004 10:30:01 AM

Here is another dual PI suggestion

-----Original Message-----
From: CATHY A. GRISBY [mailto:grisbyca@email.uc.edu]
Sent: Friday, May 07, 2004 12:11 PM
To: Petrie, Carolyn
Cc: Kurt Schibler; Ed
Subject: RE: SUPPORT Study PI, RT, Coord

Hi Carolyn,
Here is the info we have thus far of the individuals involved in Cincinnati at our 2 sites.
main PI for both--Vivek Narendran MD
Site A--University Hospital
RRT--Sandy McClanahan. We anticipate an additional RRT.
RN--Pam Krieg. Also may be another one. We are looking for representation on both AM and PM shifts.
Site C--Good Samaritan
site specific PI (for IRB purposes)--Kurt Schibler MD
RRT--Dave Mane and Eric Stephenson
NNP--Deb Riedinger, Bonnie Eilerman, Pasty Uebel
I'm sure they'll be additions and maybe some changes. I'll update as needed.
Cathy