From:	Neil Finer
To:	Wally Carlo, M.D.; ccole@bidmc.harvard.edu
Cc:	bkh@rti.org; mcw3@cwru.edu; wrich@ucsd.edu; Higgins, Rosemary (NIH/NICHD); aaf2@po.cwru.edu; edward.donovan@chmcc.org; sduara@miami.edu; poo@rti.org; Williamt@westgate.wh.usyd.edu.au; dale_phelps@urmc.rochester.edu; laskie@cochrane.co.uk; dpursley@bidmc.harvard.edu
Subject:	Re: Response to Wally Carlo on BPD assessment
Date:	Monday, July 26, 2004 7:57:11 PM

Hi Wally and Cynthia
I still remain unclear as to how this is determined. I would prefer to know the actual FiO2 above room air that is required to maintain a SpO2 of 90% or some such value as opposed to spot values of both. This score distinguishes infants on room air who have SpO2 values of 92%, 95% and 98%. Do we know what this means? I would be more comfortable knowing what the mean SpO2 was for a period of minutes/hours in a given FiO2 above room air. I can certainly understand the value of knowing the medications utilized especially if the infant is on room air. The results from an oximeter represent the averaging algorithm used, and these vary from unit to unit. These assays of SpO2 I assume, would not use the altered oximeters.
Regards
Neil
----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
To: <nfiner@ucsd.edu>; <ccole@bidmc.harvard.edu>
Cc: <bkh@rti.org>; <mcw3@cwru.edu>; <wrich@ucsd.edu>; <higginsr@mail.nih.gov>; <aaf2@po.cwru.edu>; <edward.donovan@chmcc.org>; <sduara@miami.edu>; <poo@rti.org>; <Williamt@westgate.wh.usyd.edu.au>; <dale_phelps@urmc.rochester.edu>; <laskie@cochrane.co.uk>; <dpursley@bidmc.harvard.edu>
Sent: Monday, July 26, 2004 4:35 PM
Subject: RE: Response to Wally Carlo on BPD assessment

Dear Cindy: A problem with the PROI is that the relationship between SpO2 and FiO2 will not be proportional in the ranges of FiO2 which can be used clinically. I can understand your intention to select a measure that requires minimal or no additional data collection. I think this may work to some extent (with limitations) if you limit the range of saturations acceptable to those for which PaO2 and SpO2 change simultaneously. wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, July 26, 2004 4:01 PM
To: ccole@bidmc.harvard.edu; Wally Carlo, M.D.
Cc: bkh@rti.org; mcw3@cwru.edu; wrich@ucsd.edu; higginsr@mail.nih.gov; aaf2@po.cwru.edu; edward.donovan@chmcc.org; sduara@miami.edu; poo@rti.org; Williamt@westgate.wh.usyd.edu.au; dale_phelps@urmc.rochester.edu; laskie@cochrane.co.uk; dpursley@bidmc.harvard.edu
Subject: RE: Response to Wally Carlo on BPD assessment

Hi Cynthia
What is the actual methodology of the PROI? What SpO2 is taken - the average over a 10 minute period, or some such value or a single value at a given FiO2? How reproducible is this value for a single infant over a 6, 12 or 24 hour period? Is it chart extracted from the days hourly readings?
Thanks for clarifying.
Neil

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

From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Monday, July 26, 2004 10:09 AM
To: WCarlo@peds.uab.edu; ccole@bidmc.harvard.edu; nfiner@ucsd.edu
Cc: bkh@rti.org; mcw3@cwru.edu; wrich@ucsd.edu; higginsr@mail.nih.gov; aaf2@po.cwru.edu; edward.donovan@chmcc.org; sduara@miami.edu; poo@rti.org; Williamt@westgate.wh.usyd.edu.au; dale_phelps@urmc.rochester.edu; laskie@cochrane.co.uk; dpursley@bidmc.harvard.edu; nfiner@ucsd.edu
Subject: Response to Wally Carlo on BPD assessment

Dear Wally,
Thank you for your email.

The proposed POST ROP OI (PROI) is simply the FiO2/SpO2.
It does not need mean airway pressure, paO2, etc. (which is necessary for the original OI). Use of the PROI + PAS would provide an index of severity and use readily avaiable data. Neither of these measures requires ABG or mean airway pressure.

The proposed PROI and the PAS are suggestions as to how we may objectively and simply assess the severity of BPD at 36 wk and maximize having complete data in the most feasible manner possible. No study to my knowledge has used PROI. I just created it last week. It is one consideration for a feasible, objective measure of BPD at 36 wk. It can be calculated with masked Masimo monitor (corrected for offset) or with routine NICU oximeter.

A logistial problem with the physiologic assessment BPD is compliance with this procedure if infants are in community hospitals. Thus, one may have more missing data for the outcome measure.

For PROI and PAS, the data exist in nursing flow sheet and medical chart: the simultaneous FiO2/SpO2 and the components of PAS (FiO2, MV, CPAP, meds) at 36 wk. These data are not dependent upon someone remembering to do the physiologic test at 36 wk.

PROI does assume the infant is on a pulse oximeter. If an infant is on room air and not on an oximeter (e.g. at home), one can impute a PROI<0.233 and still calculate the PAS based on parent's history of meds.

I hope this helps. Comments are encouraged. Thank you for yours.
- Cynthia

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 22, 2004 6:34 PM
To: ccole@bidmc.harvard.edu; nfiner@ucsd.edu
Cc: bkh@rti.org; mcw3@cwru.edu; wrich@ucsd.edu; higginsr@mail.nih.gov; aaf2@po.cwru.edu; edward.donovan@chmcc.org; sduara@miami.edu; poo@rti.org; Williamt@westgate.wh.usyd.edu.au; dale_phelps@urmc.rochester.edu; laskie@cochrane.co.uk; dpursley@bidmc.harvard.edu
Subject: RE: Response to Neil Finer on BPD assessment

Cynthia: A problem with the PROI would be the need for mean airway pressure for the calculation but many babies would be off vent/CPAP. An alternative would be AaDO2 or a/A ratio and use vent/CPAP and PAS, all with respective transformations (e.g. regression analysis) obtained from a subgroup

analysis. This also would not require further data collection. Wally

-----Original Message-----
From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Thursday, July 22, 2004 7:24 AM
To: nfiner@ucsd.edu
Cc: bkh@rti.org; mcw3@cwru.edu; wrich@ucsd.edu; higginsr@mail.nih.gov; aaf2@po.cwru.edu; edward.donovan@chmcc.org; sduara@miami.edu; Wally Carlo, M.D.; poo@rti.org; Williamt@westgate.wh.usyd.edu.au; dale_phelps@urmc.rochester.edu; laskie@cochrane.co.uk; dpursley@bidmc.harvard.edu
Subject: RE: Response to Neil Finer on BPD assessment

Dear Neil,
Thank you for your response. This is important communication in light of the potential combination of data from different early SpO2 trials for a prospective meta-analysis (PMA).
More about the PMA in upcoming email.

Consider the following: Sum POST ROP OI and Pulmonary Acuity Score (from STOP ROP). This 'PROI+PAS' score combines a patient's oxygenation response at a specific FiO2 (POST ROP OI)with the respiratory support/ meds (PAS) that an infant is receiving at any age one chooses (32 wk, 36 wk, 38 wk, at discharge). The PROI+PAS should require no additional data collection since these data are part of the pulse oximeter and/or medical record.

In response to Lisa'Askies question, 'What if a baby is breathing room air and does not have a pulse oximeter at 36 wk (or other GA equivalent) or is at home on RA.
I recomend that we impute a PROI value < or = min PROI + PAS. There is no need to expend the energy, time, and expense of study coordinators nurses, or parents in obtaining SpO2 readings on a baby who is doing that well (especially if they are at home).

The choice of averaging 4 PROI readings was to simply not base the PROI on just 1 or 2 SpO2 readings.
Perhaps three SpO2 readings are reasonable for an infant who is on supplemental oxygen and a pulse oximeter. Any scoring and definition will have its limitations. We need to keep it simple.

I always appreciate your thoughts. I will be away July 22-25.
Will speak with you next week.
- Cindy

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, July 22, 2004 12:24 AM
To: ccole@bidmc.harvard.edu
Cc: Betty Hastings; Michele Walsh; Wade Rich; Rosemary Higgins; Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Ken Poole
Subject: Re: Response to Lisa Askie's comments on BPD assessment

Hi Cynthia
We will continue the study oximeters till the infants is off of oxygen or till 36 weeks of age, whichever is the shorter. Our study will use the Physiologic Definition at 36 weeks for infants still requiring oxygen, which will entail a forced removal of oxygen for infants requiring < 30% oxygen using previous Network criteria. We will do the challenge with non-altered

oximeters. I will be interested in your groups final deliberations on these issues. Be well Neil
----- Original Message -----
From: <ccole@bidmc.harvard.edu>
To: <laskie@cochrane.co.uk>; <ccole@bidmc.harvard.edu>; <Alan.jobe@chmcc.org>; <solimano@unixg.ubc.ca>; <Anne@ctc.usyd.edu.au>; <alindblad@emmes.com>; <acaponejr@yahoo.com>; <augusto_sola@oz.ped.emory.edu>; <balaji.swami@cshs.org>; <Schmidt@mcmaster.ca>; <Bvohr@wihri.org>; <bmackinnon@tufts-nemc.org>; <brian.darlow@chmeds.ac.nz>; <Brian.Fleck@luht.scot.nhs.uk>; <Charles.simmons@cshs.org>; <Christian-F.Poets@med.uni-tuebingen.de>; <Dammann.Christiane@mh-hannover.de>; <Colin.morley@wch.org.au>; <dale_phelps@urmc.rochester.edu>; <Dhs@perinatal.usyd.edu.au>; <david.hunter@childrens.harvard.edu>; <Dkwallac@med.unc.edu>; <pillersd@ohsu.edu>; <Deborah.Vanderveen@childrens.harvard.edu>; <dpursley@bidmc.harvard.edu>; <DIAZJOSE@clap.ops-oms.org>; <Shey@easynet.co.uk>; <sgabai@caregroup.harvard.edu>; <h.halliday@qub.ac.uk>; <Sinclair@mcmaster.ca>; <Horbar@VTOXFORD.org>; <Jhagadorn@tufts-nemc.org>; <Kiani@masimo.com>; <Jtf38@columbia.edu>; <John@ctc.usyd.edu.au>; <Keith.barrington@mcgill.ca>; <Kenneth.Wright@cshs.org>; <lwd@unimelb.edu.au>; <mmoro@med.ucm.es>; <MSayre@masimo.com>; <mmccormi@hsph.harvard.edu>; <mcallen@jhmi.edu>; <Mxh7@cwru.edu>; <maximo.vento@uv.es>; <mrepka@jhmi.edu>; <Mpetters@masimo.com>; <mikko.hallman@oulu.fi>; <Noden@emmes.com>; <nfiner@ucsd.edu>; <neil.marlow@nottingham.ac.uk>; <neil.mcintosh@ed.ac.uk>; <paneth@epi.msu.edu>; <o.d.saugstad@medisin.uio.no>; <peter.brocklehurst@perinat.ox.ac.uk>; <p.davis@obgyn-rwh.unimelb.edu.au>; <info@profox.net>; <saundric@musc.edu>; <Wcarlo@peds.uab.edu>; <Good@Ski.org>; <bill.hay@uchsc.edu>; <Williamt@westgate.wh.usyd.edu.au>; (b) (6) [redacted] <wotm@optusnet.com.au>
Sent: Wednesday, July 21, 2004 2:30 PM
Subject: Response to Lisa Askie's comments on BPD assessment

> Dear Lisa,
> Thank you for your helpful comments. Consistent data collection is
> essential.
>
> The discussions regarding CLD or BPD assessment at 36 wk are important
> and necessary.
> It is also important to emphasize, as noted by Brian Darlow, that we
> not become too distracted on details of a secondary outcome (e.g. CLD)
> at this time. The long term outcomes, ophthalmic issues, and
> prospective meta-analysis are very important areas on which to focus
> attention. Thank you, Brian.
>
> To respond to your comments, Lisa re: BPD:
> The data necessary for assessing BPD at 36 wk sould be data that is
> routinely available. Obviously, if an infant is in room air and not on
> a
> SpO2 monitor at 36 wk, then we could decide that that is a criteria
> for no BPD or do spot check of SpO2. The proposal to average PROI over
> 4 readings at specific times was an attempt to get more than one SpO2,
> FiO2 reading within a 24 hours period. We can work on those details later.
>
> The simplest assessment of BPD at 36 wk would be dichotomous data: BPD
> yes = either on MV or CPAP (even if room air) or on no MV/CPAP but
with
> POST ROP OI (PROI)>0.233
> BPD no = no MV/CPAP or PROI <0.233 for infants not on MV/CPAP.

>
> The PAS score would provide a gradation of BPD severity.
>
> If the PROI were to to be used as a continuous variable for everyone
> (including those on MV and CPAP) it would obviously need to be revised
> to take into account the MV or CPAP.
> Feedback?
>
> Kind regards- Cynthia
>
>
>
> -----Original Message-----
> From: Lisa Askie [mailto:laskie@cochrane.co.uk]
> Sent: Wednesday, July 21, 2004 12:19 PM
> To: 'ccole@bidmc.harvard.edu'; Alan.jobe@chmcc.org;
> solimano@unixg.ubc.ca; Anne@ctc.usyd.edu.au; alindblad@emmes.com;
> acaponejr@yahoo.com; augusto_sola@oz.ped.emory.edu;
> balaji.swami@cshs.org; Schmidt@mcmaster.ca; Bvohr@wihri.org;
> bmackinnon@tufts-nemc.org; brian.darlow@chmeds.ac.nz;
> Brian.Fleck@luht.scot.nhs.uk; Charles.simmons@cshs.org;
> Christian-F.Poets@med.uni-tuebingen.de;
> Dammann.Christiane@mh-hannover.de;
> Colin.morley@wch.org.au; dale_phelps@urmc.rochester.edu;
> Dhs@perinatal.usyd.edu.au; david.hunter@childrens.harvard.edu;
> Dkwallac@med.unc.edu; pillersd@ohsu.edu;
> Deborah.Vanderveen@childrens.harvard.edu; dpursley@bidmc.harvard.edu;
> DIAZJOSE@clap.ops-oms.org; Shey@easynet.co.uk;
sgabai@caregroup.harvard.edu;
> h.halliday@qub.ac.uk; Sinclair@mcmaster.ca; Horbar@VTOXFORD.org;
> Jhagadorn@tufts-nemc.org; Kiani@masimo.com; Jtf38@columbia.edu;
> John@ctc.usyd.edu.au; Keith.barrington@mcgill.ca;
> Kenneth.Wright@cshs.org; lwd@unimelb.edu.au; Lisa Askie;
> mmoro@med.ucm.es; MSayre@masimo.com; mmccormi@hsph.harvard.edu;
> mcallen@jhmi.edu; Mxh7@cwru.edu; maximo.vento@uv.es; mrepka@jhmi.edu;
> Mpetters@masimo.com; mikko.hallman@oulu.fi; Noden@emmes.com;
> nfiner@ucsd.edu; neil.marlow@nottingham.ac.uk; neil.mcintosh@ed.ac.uk;
> paneth@epi.msu.edu; o.d.saugstad@medisin.uio.no;
> peter.brocklehurst@perinat.ox.ac.uk;
> p.davis@obgyn-rwh.unimelb.edu.au; info@profox.net; saundric@musc.edu;
> Wcarlo@peds.uab.edu; Good@Ski.org; bill.hay@uchsc.edu;
> Williamt@westgate.wh.usyd.edu.au; (b) (6)
> wotm@optusnet.com.au
> Subject: RE: Intervention Endpoint and Extraction of the Devil
>
>
> Cynthia,
> Whatever measure is used, it will be critical to have consistent data
> on
all
> enrolled BOOST-II/POST ROP infants for this important endpoint to
> ensure meaningful meta-analysis of data from different trials can be
achieved.
> Assessing this important outcome in this way, especially without the
> need for an air challenge test, by using data that will be routinely
> collected
on
> the vast majority of enrolled infants is an excellent suggestion.
> However,
I

> can foresee there will be some infants who will not be having this
> information collected routinely at the enrolment hospital, at this
> timepoint, so I think it is worth considering the points below.
> Clarifying these aspects of the data collection will have implications
> regarding whether the data can be treated as continuous or not in the
analysis.
>
> 1. What to do re infants already off supp O2 'permanently' (i.e. have
> been in air and off resp support for some weeks prior to the 36 wk
endpoint)?
> Should we assess all such infants at 36 weeks (i.e. put an oximeter,
> of
any
> type, on for an hour or so 4 times in the day and get the average SpO2
> value)? Or should they just be assigned an arbitrary PROI (of <0.233).
> I favour the former, but this would involve organising who is
> responsible
for
> collecting this data, especially if situations as in 2. below had
occurred.
> 2. What to do about infants already back-transferred to regional
> hospitals and/or home by this point, whether they are in oxygen or
> not? I assume
that
> for infants still in hospital but who have been back-transferred to a
> regional hospital, the enrolment hospital study coordinator would need
> to arrange getting this data from the regional hospital. This will
> require
some
> (but not a lot) of manpower. As it might not be regarded as part of
> 'routine' care for the infant at the regional hospital, the need for
> this additional assessment at 36 wks pma would need to be outlined on
> the
patient
> information sheet/consent form. What should be done about the
> (probably
very
> small) number of infants who are already at home (in air or on O2), by
> 36 wks? Again, I assume the enrolment centre research nurse/study
> coordinator would be able to organise this assessment via a home visit
> (or by
couriering
> an oximeter to the home prior to 36 wks, getting the parents to do the
> monitoring during that day, and then having the monitor couriered back
> -
as
> we did in BOOST).
> 3. What to do about the index score for infants on mechanical
> ventilation/CPAP but in air? Without adding an additional score/factor
> for this level of resp support, these infants would end up with the
> same PROI value as a well infant on no resp support and in air. For
> example, an
infant
> on CPAP but in air and saturating 93% would get the same PROI as a
> well infant on no resp support, in air, who also had a SpO2 of 93%.
> Should
those
> on mechanical ventilation be allocated a higher 'assisted ventilation
> factor' compared with CPAP only (as in the PAS score)? Or should all
> these infants just be assigned some arbitrary PROI (of >0.233). Again,

> I favour the former, but should this additional indexing be validated
> in some way first??
>
> To get dichotomous data for this outcome, defining CLD yes = either on
> MV/CPAP or PROI >0.233, and CLD no = no MV/CPAP and PROI <0.233, will
> suffice. That is, those definitely off O2 and resp support will be
> designated as CLD no, and those on MV/CPAP will be designated CLD yes,
> without any further assessments being required. However, to treat this
> outcome as (true) continuous data you will need an accurate PROI value
> for all infants, even those off O2 and resp support for some time
> before 36
wks
> (= definite no CLD using dichotomous outcome defs) and those still on
> MV/CPAP (= definite yes CLD). The logistics of this would involve
> ensuring all infants were assessed and allocated a score at 36 wks,
> including those off O2 for some time previously (and thus perhaps not
> having routine SpO2 monitoring), those already discharged from the
> enrolment hospital, and
those
> already at home, whether on or off oxygen.
>
> Thus , I think the following information needs to be collected (i.e.
> what
to
> put on the data collection sheet):
> * Mechanical ventilation: Y/N? +/- settings??
> * CPAP: Y/N +/- settings??
> * Average FiO2: (fraction) +/- form of O2 delivery (vent/CPAP
> circuit, headbox, nasal cannula - including flow rate and blend)
> * Average SpO2: (fraction)
> * Brand / type of oximeter and serial number (to enable distinction
between
> fractional and functional readings, adjusted and unadjusted oximeters
> for DCC to work out actual SpO2 reading)
>
> I think the logistics of getting an accurate PROI on all infants would
> not be too daunting as most <28 wk infants would still be having some
> form of
> SpO2 monitoring (albeit often intermittent) at 36 wks pma. The
> procedures for the different scenarios just need to be outlined
> carefully in the 'Manual of Procedures'. It would be very useful to
> have an accurately measured, continuous data outcome, collected on all
> enrolled infants, that involved very little (if any, in most cases)
> additional work for the
nursing
> staff or research assistants, and little or no disruption to the
> infants normal care at that timepoint.
>
> Well done Cynthia and team!
>
> 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
> <><><><><><><><><><><><><><><><><><>
>
> -----Original Message-----
> From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
> Sent: Tuesday, July 20, 2004 7:39 PM
> To: Alan.jobe@chmcc.org; solimano@unixg.ubc.ca; Anne@ctc.usyd.edu.au;
> alindblad@emmes.com; acaponejr@yahoo.com;
> augusto_sola@oz.ped.emory.edu; balaji.swami@cshs.org;
> Schmidt@mcmaster.ca; Bvohr@wihri.org; bmackinnon@tufts-nemc.org;
> brian.darlow@chmeds.ac.nz; Brian.Fleck@luht.scot.nhs.uk;
> Charles.simmons@cshs.org; Christian-F.Poets@med.uni-tuebingen.de;
> Dammann.Christiane@mh-hannover.de;
> ccole@bidmc.harvard.edu; Colin.morley@wch.org.au;
> dale_phelps@urmc.rochester.edu; Dhs@perinatal.usyd.edu.au;
> david.hunter@childrens.harvard.edu; Dkwallac@med.unc.edu;
pillersd@ohsu.edu;
> Deborah.Vanderveen@childrens.harvard.edu; dpursley@bidmc.harvard.edu;
> DIAZJOSE@clap.ops-oms.org; Shey@easynet.co.uk;
sgabai@caregroup.harvard.edu;
> h.halliday@qub.ac.uk; Sinclair@mcmaster.ca; Horbar@VTOXFORD.org;
> Jhagadorn@tufts-nemc.org; Kiani@masimo.com; Jtf38@columbia.edu;
> John@ctc.usyd.edu.au; Keith.barrington@mcgill.ca;
> Kenneth.Wright@cshs.org; lwd@unimelb.edu.au; laskie@cochrane.co.uk;
> mmoro@med.ucm.es; MSayre@masimo.com; mmccormi@hsph.harvard.edu;
> mcallen@jhmi.edu; Mxh7@cwru.edu; maximo.vento@uv.es; mrepka@jhmi.edu;
> Mpetters@masimo.com; mikko.hallman@oulu.fi; Noden@emmes.com;
> nfiner@ucsd.edu; neil.marlow@nottingham.ac.uk; neil.mcintosh@ed.ac.uk;
> paneth@epi.msu.edu; o.d.saugstad@medisin.uio.no;
> peter.brocklehurst@perinat.ox.ac.uk;
> p.davis@obgyn-rwh.unimelb.edu.au; info@profox.net; saundric@musc.edu;
> Wcarlo@peds.uab.edu; Good@Ski.org; bill.hay@uchsc.edu;
> Williamt@westgate.wh.usyd.edu.au;(b) (6) [redacted]
> wotm@optusnet.com.au
> Subject: Intervention Endpoint and Extraction of the Devil
> Importance: High
>
> << File: Cole's synthesis and response 72004 send.doc >> Dear POST
> ROP Colleagues, Thank you for an informative exchange.
> The attachment contains the following:
>
> Synthesis of the Intervention endpoint.
> Proposal for BPD definition. Includes proposed POST ROP Oxygenation
> Index (POST ROP OI). Conversion equation for NC O2 flow to FiO2
equivalent.
> Pulmonary Acuity Score from STOP ROP trial.
>
> I fully expect (and want) another round of vigorous response. I will
> will respond to your emails as much as possible as soon as possible.
> (b) (6) [redacted] regular
internet
> connection, I will be back in touch then.

>
> Thank you again for your collaboration on this issue.
> Cynthia
>
>
>
> Future POST ROP issues:
> Outcome assessment: Timing, tool(s), definitions Opthalmic issues
> Results of the NIH review
>
> Stay tuned-
>
> <<Cole's synthesis and response 72004 send.doc>>
>

Incoming mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.723 / Virus Database: 479 - Release Date: 7/19/2004

Outgoing mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.723 / Virus Database: 479 - Release Date: 7/19/2004

Incoming mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.723 / Virus Database: 479 - Release Date: 7/19/2004

Outgoing mail is certified Virus Free.
Checked by AVG anti-virus system (http://www.grisoft.com).
Version: 6.0.723 / Virus Database: 479 - Release Date: 7/19/2004

From: Wade Rich
To: Higgins, Rosemary (NIH/NICHD)
Cc: "Neil Finer"
Subject: RE: Cost of Masimo sensors for SUPPORT
Date: Tuesday, July 20, 2004 2:00:05 PM

We have proposed 200 oximeters for SUPPORT, with 50 backup.

We currently have 16 centers who enroll an averave of 4+ infants <1000 grams per month. Some centers
have had 12 in a month.
If we just spread out the oximeters evenly over all sites, each will get 12 oximeters.
Using the worst case 36 week stopping point, and worst case 24 week GA, each infant could need the oximeter
for 12 weeks.

Every three months, 4 oximeters would be taken off and be ready for the current month. Life would be
a bed of roses for sites that enroll 4 babies.

However, if Dr. Carlo has a couple of months with 12 subjects, he is hosed. I think rather than have a bunch
of oximeters sitting at RTI or Masimo waiting to be shipped, we might be better off "overstocking" the 4 largest
enrollers with 5 extra units each, and keeping only 30 on standby.

We have played this pretty close so as not to spend too much money. That being said, I believe that during "peak season" we might be in trouble.

Wade

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Issues
Date: Tuesday, July 20, 2004 1:34:57 PM

Thanks Rose

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 20, 2004 7:14 AM
To: 'nfiner@ucsd.edu'
Subject: Re: SUPPORT Issues

Neil
I think 36 weeks or off oxygen is fine - I also sent it to Dale Phelps for a curbside comment on the rop issue.

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>; 'Betty Hastings' <bkh@rti.org>; 'Ken Poole' <poo@rti.org>; 'Michele' <mcw3@po.cwru.edu>
Sent: Tue Jul 20 09:59:29 2004
Subject: SUPPORT Issues

Hi Everyone

One more issue

- When to stop the study oximeters. I think our choices are 36 weeks after the physiologic, or when out of oxygen. After 36 weeks simplifies the use the monitors and allows predictability for re-use, whereas till out of oxygen maintains the bias in FiO2 till discharged. I am in favor of stopping after 36 weeks and the physiologic definition, and then converting to a standard oximeter if still needed. Could you please send me your thoughts here? The POST ROP group is debating this issue, and is considering stopping at 32 weeks. I believe that we need to go beyond this to our primary. I believe that the ongoing use of a higher SpO2/FiO2 has already been addressed by STOP-ROP and BOOST, and that the continuation will only somewhat complicate our study. In addition, I doubt that anyone would want to discharge an infant without knowing the actual SpO2 at discharge and thus a conversion will occur at some time in infants who still require Oxygen. There will be a lesser number obviously if we wait till discharge.

- I vote 36 weeks after the physiologic. Please send me your vote here.

- Thanks

- Neil

From: Neil Finer
To: "Michele Walsh"
Cc: "Shahnaz Duara"; Avroy A. Fanaroff, M.D.; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD); "Neil Finer"; "Wade Rich"; "Betty Hastings"; "Ken Poole"
Subject: RE: SUPPORT Issues
Date: Tuesday, July 20, 2004 1:28:29 PM

Ni Michele.
We will use the standard approach using non-altered oximeters. 90% is fine.
Neil

-----Original Message-----
From: Michele Walsh [mailto:mcw3@po.cwru.edu]
Sent: Tuesday, July 20, 2004 10:25 AM
To: nfiner@ucsd.edu; 'Shahnaz Duara'; Avroy A. Fanaroff, M.D.; 'Ed Donovan'; higginsr@mail.nih.gov; 'Wade Rich'; 'Betty Hastings'; 'Ken Poole'
Subject: Re: SUPPORT Issues

I agree with stopping the oximeter at 36 wks.
One issue with physiologic:
The P/F definition is currently set at 90% sat.
Is that the sat cut point desired for SUPPORT?
Michele

----- Original Message -----
From: Neil Finer
To: 'Shahnaz Duara' ; Avroy A. Fanaroff, M.D. ; 'Ed Donovan' ; higginsr@mail.nih.gov ; 'Neil Finer' ; 'Wade Rich' ; 'Betty Hastings' ; 'Ken Poole' ; 'Michele'
Sent: Tuesday, July 20, 2004 9:59 AM
Subject: SUPPORT Issues

Hi Everyone
One more issue

- When to stop the study oximeters. I think our choices are 36 weeks after the physiologic, or when out of oxygen. After 36 weeks simplifies the use the monitors and allows predictability for re-use, whereas till out of oxygen maintains the bias in FiO2 till discharged. I am in favor of stopping after 36 weeks and the physiologic definition, and then converting to a standard oximeter if still needed. Could you please send me your thoughts here? The POST ROP group is debating this issue, and is considering stopping at 32 weeks. I believe that we need to go beyond this to our primary. I believe that the ongoing use of a higher SpO2/FiO2 has already been addressed by STOP-ROP and BOOST, and that the continuation will only somewhat complicate our study. In addition, I doubt that anyone would want to discharge an infant without knowing the actual SpO2 at discharge and thus a conversion will occur at some time in infants who still require Oxygen. There will be a lesser number obviously if we wait till discharge.
- I vote 36 weeks after the physiologic. Please send me your vote here.
- Thanks
- Neil

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD); "Wade Rich"; Hastings, Betty J.
Subject: RE: Cost of Masimo sensors for SUPPORT
Date: Monday, July 19, 2004 9:45:32 AM
Attachments: Contacts_Coordinators[7-19-04].doc

Wade,
Here is a listing of all Coordinators with addresses, etc.
Will coordinators be sent an order form to complete? This is how we have done this type of thing in the past. If you can send me the order form, I can send it to the sites. Thanks.
Betty

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 19, 2004 8:56 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

****

Center 09: Emory University

Ellen Hale, R.N.C., B.S.
Division of Neonatology
Grady Memorial Hospital
P.O. Box 26015
80 Butler Street, Room D1504
Atlanta, GA 30335
Phone: (404) 616-4218
FAX: (404) 524-3953
E-Mail: ellen_hale@oz.ped.emory.edu

Center 11: University of Cincinnati

Cathy Grisby, R.N.
College of Medicine
Department of Pediatrics
University of Cincinnati
P.O. Box 670541
Cincinnati, OH 45267-0541
Phone: (513) 558-0005
FAX: (513) 558-7770
E-Mail: grisbyca@email.uc.edu

Center 12: Indiana University

Lucy Miller, R.N.
Perinatal Medicine Section
Indiana University
Department of Pediatrics
699 West Drive, RR-208
Indianapolis, IN 46202-5119
Phone: (317) 278-7809
FAX: (317) 274-4759
E-Mail: lucmille@iupui.edu

Center 13: Yale University

Pat Gettner, R.N.
Yale-New Haven Children's Hospital
20 York St. WP493
New Haven, CT 06504
Phone: (203) 688-7987
FAX: (203) 688-5426
E-Mail: pat.gettner@yale.edu

Center 14: Brown University

Angelita Hensman, R.N.C.
Department of Pediatrics
Women & Infant's Hospital
101 Dudley Street, Room 1130, 1st Floor
Providence, RI 02905
Phone: (401) 274-1122
FAX: (401) 453-7571
E-Mail: ahensman@wihri.org

Center 15: Stanford University

M. Bethany Ball, R.N.
Stanford University
Division of Neonatology
750 Welch Road, Suite 315
Palo Alto, CA 94304
Phone: (650) 725-8342
FAX: (650) 725-8351
E-Mail: mbball@leland.stanford.edu

Center 16: University of Alabama

Monica Collins, RN, MaEd
Division of Neonatology
University of Alabama at Birmingham
Suite 525 New Hillman Bldg.
619 S 20th Street
Birmingham, AL 35233-7335
Phone: (205) 934-5771
FAX: (205) 934-3100
E-Mail: mcollins@peds.uab.edu

Center: 18 University of Texas at Houston

Georgia McDavid, RN
Department of Pediatrics
University of Texas-Houston
6431 Fannin, Suite 3.252, Medical Sciences Building
Houston, TX 77030-1501
Phone: 713-500-5734
Fax:713-500-5794
E-Mail: gmcdavid@ped1.med.uth.tmc.edu

Center: 19 Duke University

Kathy Auten, R.N.
Division of Neonatology
Duke University Medical Center
Box 3179
204 Bell Building
Durham, NC 27710
Phone: (919) 681-5859
FAX: (919) 668-3361
E-mail: auten002@mc.duke.edu

Center: 20 Wake Forest University

Nancy Peters, R.N.
Dept. of Pediatrics
WFU School of Medicine
Medical School Blvd.
Winston-Salem, NC 27517
Phone: (336) 716-6911
FAX: (336) 716-2525
E-Mail: npeters@wfubmc.edu

Center: 21 University of Rochesters

Linda Rubens, R.N.
Division of Neonataology
Children's Hospital at Strong
601 Elmwood Ave., Box 651
Rochester, NY 14642
Phone: (716) 275-0218
FAX: (716) 461-3614
E-Mail: linda_rubens@urmc.rochester.edu

Center: 22 University of California--San Diego

Wade Rich
University of California--San Diego
200 W. Arbor Drive, 8774
San Diego, CA 9103-8774
Phone: (619) 543-3759
E-Mail: wrich@ucsd.edu

July 19, 2004

Contacts for the Network Study

Center 03: Case Western Reserve University

Nancy Newman, R.N.
University Hospitals of Cleveland
Rainbow Babies & Children's Hospital
11100 Euclid Ave., Room 3100
Cleveland, OH 44106-6010
Phone: (216) 368-3084
FAX: (216)844-3380
E-mail: nxs5@po.cwru.edu

Center 04: University of Texas

Gay Hensley, R.N.
Department of Pediatrics
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., E3 404
Dallas, Texas 75235-9063
Phone: (214) 648-3780
FAX: (214) 648-2481
E-mail: gaynelle.hensley@utsouthwestern.edu

Center 05: Wayne State University

Rebecca Bara, R.N.
Division of Neonatal & Perinatal Medicine
Children's Hospital of Michigan
3901 Beaubien Blvd.
Detroit, MI 48201
Phone: (313) 745-5843
FAX: (313) 745-5867
E-mail: ae5357@wayne.edu

Center 08: University of Miami

Ruth Everett, R.N.
University of Miami
Dominion Towers, 8th Floor (M827)
1400 NW 10th Avenue
P.O. Box 016960
Miami, Fl 33136
Phone: (305) 243-6884
FAX: (305)243-6581
E-mail: Reverett@med.miami.edu

From: Neil Finer
To: "Wally Carlo, M.D."; "Edward Donovan"; aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); reverett@med.miami.edu; sduara@miami.edu; mcw3@po.cwru.edu; petrie@rti.org; poo@rti.org; wrich@ucsd.edu
Cc: "Diane Timmer"; mlg@cwru.edu; "Marsha Sumner"; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
Subject: RE: SUPPORT Conf call - Mon July 19, 1pm EDT (10am PDT)
Date: Friday, July 16, 2004 5:01:59 PM

I agree. Should we also consider a significantly increased ROP occurrence in the Hi vs Low SpO2 arm?
I would suggest a P value<0.001 for ROP requiring laser.
I would agree to keep recruiting 1 arm if the other is stopped unless the adverse event was significant overall.
Talk to you on Monday
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, July 16, 2004 12:53 PM
To: Edward Donovan; aaf2@cwru.edu; higginsr@mail.nih.gov; reverett@med.miami.edu; sduara@miami.edu; mcw3@po.cwru.edu; petrie@rti.org; poo@rti.org; nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Diane Timmer; mlg@cwru.edu; Marsha Sumner; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
Subject: RE: SUPPORT Conf call - Mon July 19, 1pm EDT (10am PDT)

I agree with the idea of continuing enrollment in one arm if enrollment is put on hold on the other. wally

---

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Friday, July 16, 2004 2:41 PM
To: aaf2@cwru.edu; higginsr@mail.nih.gov; reverett@med.miami.edu; sduara@miami.edu; Wally Carlo, M.D.; mcw3@po.cwru.edu; petrie@rti.org; poo@rti.org; nfiner@ucsd.edu; wrich@ucsd.edu
Cc: Diane Timmer; mlg@cwru.edu; Marsha Sumner; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
Subject: RE: SUPPORT Conf call - Mon July 19, 1pm EDT (10am PDT)

Talking points:

I like 1/1000 alpha error rate for early stop for efficacy.

for O2 sat arm, I would use severe IVH as stopping for harm. maybe also highly stat. sig. long duration desats < 80%

for CPAP arm: pneumothorax or definite PIE, large diff. (RR = 0.5) and low p 0.01.
also nasal septum necrosis with loss of septum; incidence > 0.05 and low p 0.01

I think that we should keep recruiting for the other arm if one is put on hold.

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

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 07/16/2004 12:45:28 PM >>>
Ed
Stopping early for efficacy may require a very significant p value (I.e. < 0.005 or < 0.001) - how strict should one be?

What "harm" items other than death or severe ROP would you include? IVH (severe grade)?, etc.

We should be prepared to continue one arm if another arm is stopped - I think Dale Phelps had mentioned this at one of the Steering Committee meetings.

Putting recruitment "on hold" may be another alternative, especially as it takes children up to 13 weeks or so to reach status. What if one arm is halted - what do we do with the other arm??

We have also talked about air leak as a serious adverse outcome and how should this be factored into the safety of the trial?

If people would like to continue the email dialogue, our call on Monday may be more productive.

Thanks
Rose

> -----Original Message-----
> **From:** Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> **Sent:** Friday, July 16, 2004 12:37 PM
> **To:** aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); reverett@med.miami.edu; sduara@miami.edu; wcarlo@peds.uab.edu; petrie@rti.org; poo@rti.org; nfiner@ucsd.edu; wrich@ucsd.edu
> **Cc:** Diane Timmer; mlg@cwru.edu; msumner@peds.uab.edu; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
> **Subject:** RE: SUPPORT Conf call - Mon July 19, 1pm EDT (10am PDT)
>
> Vivek Narendran, co-site-PI for SUPPORT in Cincinnati, will be attending for me.
>
> Key principles from my perspective:
>
> Very conservative p values should be used but these might vary by outcome, for example lower for efficacy and higher for safety.
>
> Stopping early for efficacy in my mind is only necessary when the outcome is death or lifelong severe handicap. If we're going to stop early for efficacy, we should use a p value no higher than 0.01.
>
> Stopping early for safety would vary by harm variable:
>
> Death should have high p (0.05?)
> Severe ROP, ie laser, might have a lower p
> I'm not sure how to address harm that has no logical association with either intervention. We need to look for these, but perhaps the DSMC should be responsible for stopping rules for these?
>
> Are we prepared to continue one arm if stopping rules are met for the other?
>
> We might want to discuss temporary stopping versus irreversible stopping (lesson learned

from PINO).

Let me know if there are any other issues that you would like me to chime in on.

Have a good discussion.
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

>>> "Petrie, Carolyn" <petrie@rti.org> 07/14/2004 4:42:59 PM >>>
Reminder for the SUPPORT stopping rules call. If you are unable to attend, please circulate your written comments to the group, prior to the call. Thank you!

The SUPPORT conference call to discuss stopping rules for this trial is scheduled for
Monday July 19
1:00 PM ET (10:00 AM PT)

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: (b) (6) when prompted)

Leader: Rose Higgins

Carolyn Petrie

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

From: Neil Finer
To: ccole@bidmc.harvard.edu
Cc: "Shahnaz Duara"; Avroy A. Fanaroff, M.D.; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD) [E]; "Neil Finer"; "Wade Rich"; "Betty Hastings"; "Ken Poole"; "Michele"
Subject: RE: Intervention endpoint
Date: Friday, July 16, 2004 11:38:51 AM
Attachments: Intervention Endpoint 071504.doc

Hi Cynthia
Thanks you for including me in this discussion.
We are also somewhat debating this issue, but only as to whether the intervention should continue to 36 weeks and the physiologic and clinical diagnosis of BPD, or till the end of oxygen use whichever is the longer. As we are looking at BPD diagnosed using the oxygen requirement at 36 weeks and the physiologic definition, involving an attempt at discontinuing oxygen if the FiO2 is low, we believe that the intervention should continue to this outcome. This certainly leaves open the issue of continuing the treatment with the altered Oximeters which may affect ongoing ROP in those infants whose disease is not resolved. Another approach being considered is to continue the intervention beyond 36 weeks only in infants who still require supplemental oxygen, and whose eyes have not yet reached maturity, ie 2 stage 3 examinations. This would drastically reduce the number of infants who would need to continue on the oximeter.
We believe that this study will not provide additional useful information on the treatment of established ROP more than was available from STOP-ROP or BOOST trials.
We are having a conference call on Monday and I will share with you our decision.
Good luck
Neil Finer

-----Original Message-----
From: ccole@bidmc.harvard.edu [mailto:ccole@bidmc.harvard.edu]
Sent: Thursday, July 15, 2004 2:49 PM
To: Alan.jobe@chmcc.org; solimano@unixg.ubc.ca; Anne@ctc.usyd.edu.au; alindblad@emmes.com; acaponejr@yahoo.com; augusto_sola@oz.ped.emory.edu; balaji.swami@cshs.org; Schmidt@mcmaster.ca; Bvohr@wihri.org; bmackinnon@tufts-nemc.org; brian.darlow@chmeds.ac.nz; Brian.Fleck@luht.scot.nhs.uk; Charles.simmons@cshs.org; Christian-F.Poets@med.uni-tuebingen.de; Dammann.Christiane@mh-hannover.de; ccole@bidmc.harvard.edu; Colin.morley@wch.org.au; dale_phelps@urmc.rochester.edu; Dhs@perinatal.usyd.edu.au; david.hunter@childrens.harvard.edu; Dkwallac@med.unc.edu; pillersd@ohsu.edu; Deborah.Vanderveen@childrens.harvard.edu; dpursley@bidmc.harvard.edu; DIAZJOSE@clap.ops-oms.org; Shey@easynet.co.uk; sgabai@caregroup.harvard.edu; h.halliday@qub.ac.uk; Sinclair@mcmaster.ca; Horbar@VTOXFORD.org; Jhagadorn@tufts-nemc.org; Kiani@masimo.com; Jtf38@columbia.edu; John@ctc.usyd.edu.au; Keith.barrington@mcgill.ca; Kenneth.Wright@cshs.org; lwd@unimelb.edu.au; laskie@cochrane.co.uk; mmoro@med.ucm.es; MSayre@masimo.com; mmccormi@hsph.harvard.edu; mcallen@jhmi.edu; Mxh7@cwru.edu; maximo.vento@uv.es; mrepka@jhmi.edu; Mpetters@masimo.com; mikko.hallman@oulu.fi; Noden@emmes.com; nfiner@ucsd.edu; neil.marlow@nottingham.ac.uk; neil.mcintosh@ed.ac.uk; paneth@epi.msu.edu; o.d.saugstad@medisin.uio.no; peter.brocklehurst@perinat.ox.ac.uk; p.davis@obgyn-rwh.unimelb.edu.au; info@profox.net; saundric@musc.edu; Wcarlo@peds.uab.edu; Good@Ski.org; bill.hay@uchsc.edu; Williamt@westgate.wh.usyd.edu.au; (b) (6) wotm@optusnet.com.au
Cc: sgabai@caregroup.harvard.edu
Subject: Intervention endpoint

Importance: High

Dear POST ROP Planning Group,

As noted in my email to you on July 8, 2004, as a Planning Group, we will address and strive to resolve one specific protocol issue per email in a series of separate emails. During this process, please do not lose sight of all the issues on which we agree and how much progress has truly been made.

We are all aware, in any clinical trial, there are competing scientific, ethical, and practical goals. What concessions can and can't be made? Our goal is to choose the most feasible, pragmatic, efficient, cost effective study that is ethically, scientifically sound design and will answer the question most accurately with least bias.

The attachment in this email only addresses "Intervention endpoint". After you consider the 3 intervention endpoints ('32 wk"; '36 wk; or 'when weaned to room air'), please respond as to which endpoint is preferred, acceptable, and not acceptable to you and your center/country. If this question is not relevant to you, please respond 'no opinion'. Comments are always invited. Please forward, as early as is feasible, your response to my assistant, Sandy Gabai (sgabai@bidmc.harvard.edu).

Thank you- Cynthia

Cynthia H. Cole, MD, MPH,
Director of Research
Department of Neonatology,
Beth Israel Deaconess Medical Center
330 Brookline Avenue, Boston, MA 02115
phone: USA code+ 617-667-3276
FAX: USA code + 617-667-7040
email: ccole@bidmc.harvard.edu

<<Intervention Endpoint_071504.doc>>

July 15, 2004

POST ROP/ BOOST II
Intervention Endpoint

Biological, Clinical, Feasibility, and Financial Considerations (potential advantages and disadvantages) of '32 wk' vs. '36 wk' vs. 'when infant weans to room air.'

Biological, clinical considerations: First, no one knows with certainty what are biological, clinical benefits, risks, or tradeoffs of the 3 proposed durations of intervention. Whatever endpoint is chosen, we must be clear that what is being tested is a strategy of targeting SpO2 85-89% compared to 91-95% from early in the neonatal course (<24 hrs age) through a specified intervention endpoint.

The strongest biological, clinical consideration favoring 'until weaned to Room Air' endpoint is that this endpoint most closely mimics current clinical care. The following comment by one member summarizes the scientific rationale for **'until weaned to Room Air'** endpoint:

"I tend to the view that we should, in a pragmatic trial that aims to guide future practice, mirror current practice as closely as possible, and this would mean continuing the differences for as long as they would have been continued in real life -which is until added oxygen is discontinued, in hospital or at home. I was fascinated by the possibility raised in the literature review from the POST ROP and BOOST II applications that a few extra percent of FiO2 for a few extra weeks could significantly exacerbate pulmonary and cerebral oxidative damage. To define the true extent of any differences in chronic oxygen dependency and neuro-developmental impairment by mirroring current practice would be important in estimating the long
term economic impact and in informing parental choices over what may prove to be competing adverse outcomes."

The pragmatic benefits of '36 wks' vs. 'until weaned to room air' endpoint in terms of cost and feasibility are considerable. The pragmatic benefits of '32 weeks endpoints' are even greater. Thus, logistics, feasibility, and financial implications of longer endpoints must be carefully considered. These are summarized below.

Biological, clinical considerations for 32 wk GA endpoint: Infants at highest risk for severe ROP [23-25 wk gestation infants in POST ROP/BOOST II countries] would be in their assigned SpO2 range for 7-9 weeks through 32 wk equivalent GA (unless they weaned to room air earlier); infants born 26<28 wk GA, and at somewhat less risk of severe ROP, would be in assigned range a maximum of 6 to 4 weeks, respectively. Some investigators consider that 32 wk endpoint is a reasonably acceptable duration of SpO2 targeting (if the first several postnatal weeks are indeed the critical period for reducing / inducing O2-related eye, lung, brain injury).

The issue of protocol violation for treatment of infants who develop prethreshold ROP with higher SpO2 would be less of an issue with 32 wk GA endpoint.

The '32 wk endpoint' has advantages for assessment of 'BPD at 36 weeks' off study monitor. These biological, clinical considerations regarding 32 wk endpoint' must be considered in conjunction with logistical and expense concerns noted below.

Biological, clinical considerations for 36 wk GA endpoint: The '36 wk GA endpoint' is probably a duration that would be informative regarding potential benefits, risks, or tradeoffs of the two assigned ranges. As per B Darlow, others, and myself, the scientific arguments for '36 weeks' vs 'when weaned to room air' will largely balance out.

Many infants will wean to room air before '36 wk endpoint. The "36 wk GA endpoint" will largely avoid logistical concerns of enrolled infants going home on a study monitor, but it will still have logistical and expense concerns related to transfer of infants to community hospitals (noted below).

The "36 wk GA endpoint" permits assessment of 'BPD at ~ 36 week' (within the 1st 24-72 hours off study monitor). (We will address the definition and assessment of '36 wk BPD' in a separate email. If a baby is still on oxygen in the assigned study range at 36 wk GA, then that baby would be assessed if they needed supplemental oxygen to maintain SpO2 >90% from the NICU routine pulse oximeter within the first 24 hours after discontinuing study oximeter at 36 weeks.)

Logistical considerations

Additional logistical and financial considerations are important for study centers that transfer infants to community hospitals prior to 36 weeks GA age but are able to keep infants in their Level III units through 32 weeks gestational age.

The following discussion regarding logistical / financial considerations for '32 wk' vs. '36 wk' or ' until wean to room air' endpoints are not relevant to centers that transfer infants to community hospitals prior to 32 weeks adjusted gestational age. Centers that transfer infants to community hospitals prior to 32 weeks will need to address the logistical/ financial considerations regardless of which endpoint is chosen. But, study approvals, training, data safety and monitoring plans, etc. must be in place at community nurseries before a Level III study site can transfer a study infant to that community hospital.

'32 wk endpoint' has beneficial feasibility and financial implications in a study that will undoubtedly be resource intense in effort, personnel, and money. Longer duration of intervention (i.e. 36 weeks or beyond) requires that more study sites recruit and maintain community hospitals in the study. Recruitment of community hospitals will require additional time and effort of Principal Investigators and Study Coordinators to provide initial and ongoing training of community physicians, nursing, respiratory therapists; additional effort to monitor and maximize compliance at community hospitals or home (if infant is on home O2); additional tracking of patients and monitors, more IRB approvals/ re-approvals. In addition to time and effort, participation of community hospitals will increase costs in terms of funding.

A single Level III study site that enrolls 20-30 infants per year at the Level III unit may transfer most convalescing premature infants to community hospitals, but they may transfer only 0- 4 babies per year to any individual community nursery. Thus, the same amount of effort in preparing and maintaining a hospital for the study is expended several times for 0-4 babies per community hospital. The study sites that transfer infants to community hospitals must consider if and how they can comply with completion of intervention endpoint and maintain study integrity.

Study monitor issues: 32 wk endpoint would require fewer monitors for the study (impacts expense) and would reduce logistical and expense issues of sending, returning, and tracking monitors and supplying back-up monitors for community hospitals compared to longer duration of Intervention (i.e. 36 weeks or beyond). '32 and 36 wk endpoints' reduce the logistic and compliance concerns of sending study infants home on study monitor.

'32 wk endpoint' may benefit enrollment and facilitate compliance with full duration of intervention.

Unmasking potential: Although caregivers and parents may potentially be unmasked at the **completion** of intervention at '32 wk' or '36 wk' endpoint in an infant still on supplemental oxygen, the randomization, intervention itself, and outcome assessments are still masked. We will stress the importance of not discussing their impressions with others or study personnel. This has been successfully achieved in other trials. Minimizing unmasking still needs further discussion.

Will a longer duration of intervention (≥ 36 wk) compared to '32 wk endpoint' adversely affect enrollment and participation of sites that might otherwise be solid, substantial, active contributors to the study? Even if Level III sites are eager to participate, the additional time, effort, and expense necessary to

recruit and maintain community hospitals may be a disincentive if the reality is that resources are inadequate to recruit and maintain the integrity of the study in community hospitals.

After consideration of all of these issues, several of us (B. Darlow, N. McIntosh, C Cole, and others) expressed preference for 32 weeks for scientific reasons as well as for feasibility, logistical and financial reasons. Others want to continue the study monitor for as long as the infant was in oxygen. Although the "36 wk GA endpoint" was quite a compromise for many investigators because it poses considerable logistical difficulties, there was a convergence among Planning Group members at the PAS / SPR towards 36 weeks GA endpoint for all centers.

Please provide your feedback. After we reach a consensus on this, we will move to the next issue.

Thank you- Cynthia

From: Petrie, Carolyn
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); 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: "Heidi Squibb (UCSD) (hsquibb@ucsd.edu)"; "Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)"
Subject: RE: SUPPORT Training call---Drafting the Agenda, Thur Jul 29, 11- 12pm EDT (8-9am PT)
Date: Thursday, July 15, 2004 9:46:17 AM

Hopefully this is the last email! Monday is not a good day.
We will move the call to Thursday, please see details below.

The SUPPORT Training conference call is scheduled for
Thursday July 29
11:00-12:00pm ET (8:00-9:00am PT)

The purpose of this call is to develop the training agenda (Cincinnati, Sept. 14-16).
Attached is the draft training plan.

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Please contact me if you have any questions!

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: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); 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: "Heidi Squibb (UCSD) (hsquibb@ucsd.edu)"; Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)
Subject: SUPPORT Training call---Drafting the Agenda, Mon Jul 26, 12-1pm E DT (9-10am PT)
Date: Wednesday, July 14, 2004 4:40:42 PM
Attachments: Training Plan.doc

The SUPPORT Training conference call is scheduled for
Monday July 26
12:00-1:00pm ET (9:00-10:00am PT)

The purpose of this call is to develop the training agenda (Cincinnati, Sept. 14-16). Attached is the draft training plan.

To join the call:
Dial Tollfree: **866-675**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Please contact me if you have any questions!

Carolyn Petrie

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

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: Neil Finer
To: Betty Hastings; Michele Walsh; Wade Rich; Higgins, Rosemary (NIH/NICHD) [E]; Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Ken Poole
Subject: SUPPORT Trial
Date: Wednesday, July 14, 2004 12:43:30 AM
Attachments: SUPPORT July 14 04.doc

Hello Everyone

A few issues for SUPPORT-
I have attached the now current version. This reflects the input at the Steering Committee.

Ken has modified the Statistics, Sample Size and analysis sections.

We have discussed with Ken how to label the oximeters. They come with a serial number on each piece, the base and the faceplate (Masimo calls it the "handheld"). The box containing the hand - held has the matching serial number on it. We believe that the simplest approach would be to label the box as " A " or " B " . The coordinators would have their master list identifying which serial numbers were "A" and which were "B" . These would be prepared by RTI. When an infant is removed from oxygen, that handheld is placed back in it's original box , which has already been labeled as A or B.

The next issue is the actual performance of the physiologic challenge. These should be ideally performed with non-altered oximeters. As a result, should the protocol indicate that the study oximeter will be removed at 36 weeks if the infant remains on oxygen, after the completion of the physiologic challenge using a standard oximeter. This would then result in the study being an evaluation of differing oxygen treatment up to 36 weeks. Both the BOOST and STOP-ROP have evaluated oxygen beyond 32 weeks. Do we need to continue the study oximeters beyond 36 weeks. Removal at that time would facilitate planning, and recycling within units. In addition we would have met the primary outcome for BPD. The only issue would be whether reverting to normal oximeters at this point would affect the ROP outcomes. Most of the infants affected will have already reached threshold, although not all. Can you give these issues some thought.

Abbot has pointed out that the Masimo alarms at the actual set point ie 95% and 85% and not the next lowest highest or lowest SpO2 as does the Nellcor. We will need to change the protocol to reflect these changes. We have never used the Masimo as our regular oximeter in the NICU, but it is used in our DRs, but without alarm settings in that environment.

Ken, can you look at the only highlighted area on page 20, Section 4.4. We discussed this at the Steering Committee. Are you OK with this wording. Do you want to change this?

Next Betty sent a query regarding getting consents and that at one center were concerned that some Moms and their babies may be too sick to approach. I am copying you with my reply. Please let me know your thoughts. We are going to ask for a deferred consent here at UCSD for Parents whom we cannot consent, much the same as for the DR CPAP trial. However, I am going to use the SAFE trial approach as indicated in my response to Betty.

Hi Betty
I think that there are a number of possibilities.
1. Discuss with the OBs why they would want to exclude any babies from such a trial.

2. Explore the use of a deferred consent as was used for the Adult Albumin Trial – SAFE Trial NEJM May 27, 2004 – We are going to try to use this at UCSD. This would involve attempting to consent all eligible Moms, but those that are unable to be consented would have the initial resuscitation intervention, and then attempt to approach a responsible parent to allow the infant to remain in the trial or not. This would involve randomizing the infant to either CPAP or early Surfactant, both currently utilized practices for the ELBW infant.
3. We believe that a waiver would be difficult here especially for the use of the altered oximeters, but some centers may approve.
4. Include the description of the study in prenatal counseling.

Ed sent the results of his CPAP survey which is very helpful. Thanks for doing this Ed. I will ask Wade to get samples of the various nasal prongs to units that have no any experience with them. He has been in correspondence with the centers as well. I agree that we should not concentrate on the pressure delivery device. We also need to develop various strategies for initiating DR CPAP. Sites can use a mask for initiation and transfer to the NICU or apply the nasal prongs in the DR. For each center this may depend on where the DR resuscitation site is relative to the NICU, and how this room is equipped etc. I would also like the sites that haven't used much CPAP to start now and gain some further experience with CPAP in the ELBW infant. The easiest approach may be to use at extubation. Ed, who are the 4 units who have less than 10 cases per month? I would also like to know the units that have no experience with DR CPAP. They may be worth a site visit. Ed can you send me those?
We will talk next Monday. If you have any issues that you want added to our agenda, let me know.
Hope that you having a great summer.
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
July 14, 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

Randomization will be stratified by gestational age group , will occur prior to delivery for consented deliveries, and will be performed by utilizing specially prepared double-sealed envelopes. Deliveries will be randomized as a unit, thus multiples, twins, triplets etc will be randomized to the same arm of the trial. We believe that this methodology will improve the percentage of consents, since in previous trials parents of multiple infants have expressed concern that their infants were being randomized to different treatment arms. We have made an appropriate sample size adjustment to account for this clustering effect.

Each randomization will indicate either Treatment Group (CPAP and permissive ventilation management) or Control Group (Prophylactic/Early surfactant and conventional ventilator management) and either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent before delivery, but the randomization envelope will only be opened when delivery is imminent for a consented family.

The Pulse Oximeters (PO) will have unique identifying labels and the oximeter specified in the randomization will be identified by a unique number which will match the number of the study Pulse Oximeter assigned for that infant. All caretakers including the coordinators will be blinded to the Pulse Oximeter range, and an identification code for each site will be maintained by the PI/Site Coordinator should identification be required for patient safety. RTI will work with Masimo to ensure that the POs are labeled with unique identifiers, whose code will identify the

actual range of the individual PO. These would be affixed prior to shipping to the sites, and a copy of the labels sent to the site would be provided to RTI.

This methodology should reduce the work load to the sites at the time of randomization, providing the care team with the information needed for the infants' randomization, and will allow the study center to be notified within 24 hours of any randomization.

3.8 Informed Consent:

Parents will be approached prior to delivery for informed consent, and their infants enrolled at delivery. As previously noted we will randomize by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery.

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours , approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 17% 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%

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 an 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 84% and 96% for both groups. The Masimo oximeters alarm at the actual alarm limit setting and not at the next lower or higher value. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable.

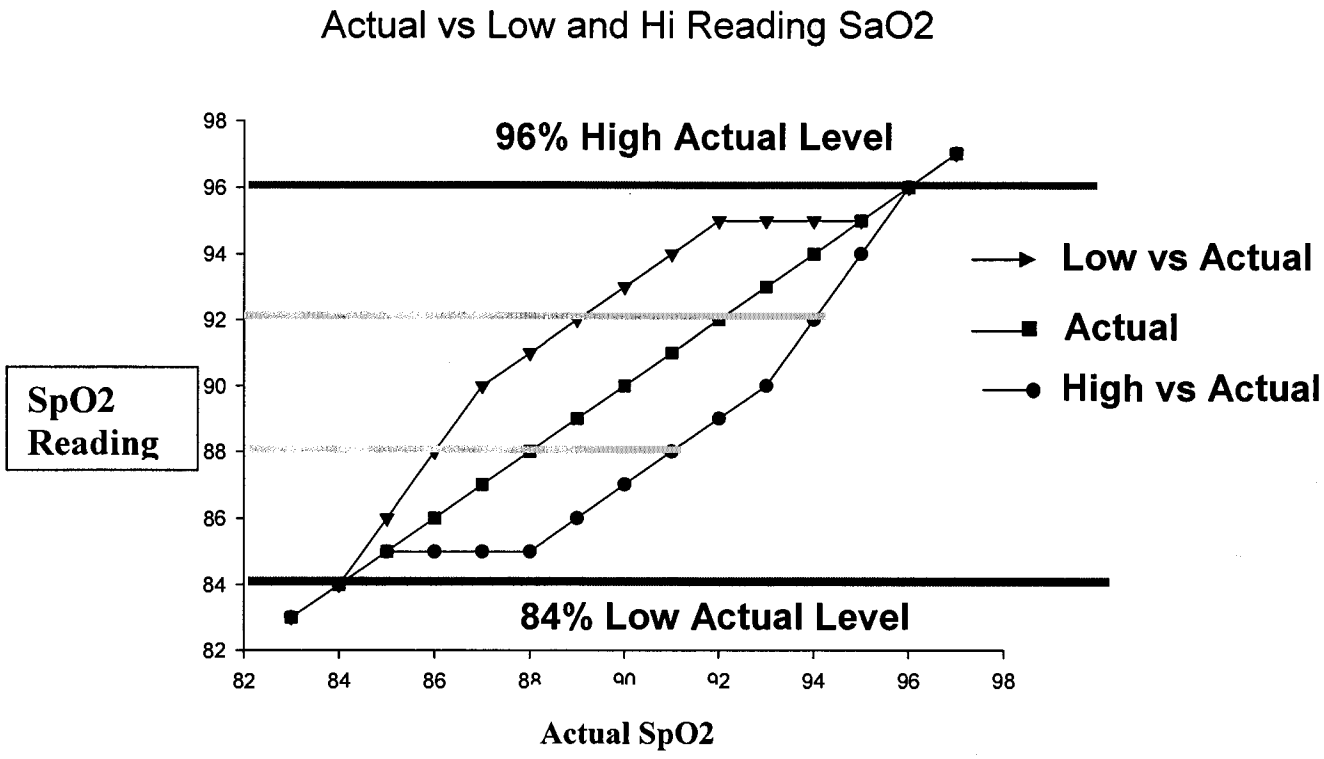
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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 79%. 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 the alarm limits of 84% and 96% 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.

Non-study pulse oximeters cannot be used on enrolled patients. If a second oximeter is required for such a patient, the site coordinator will provide an identical oximeter for the patient.

All ventilatory care after 14 days of age will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece 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.:

Post-natal Steroids

Post natal steroids for the purpose of preventing or treating BPD/CLD will be prohibited for any infant in this trial in the first 21 days of life. Hydrocortisone for hypotension may be used as noted below.

If post-natal steroid use is considered after 21 days of life for any infant for the prevention/treatment of established lung disease the following guidelines should be followed:

1. The AAP statement and recommendations regarding Post-natal steroids should be adhered to.[60]
2. The lowest dose of dexamethasone considered effective should be used and if ineffective after 24 – 48 hours they should be stopped.
3. Consider using hydrocortisone as a first therapy at a dose of 1 -2 mg/kg/day before using dexamethasone
4. For hypotension, hydrocortisone in a dose of 1 mg/kg/dose should be given after fluid administration and standard doses of ionotropes/pressors have failed to correct the low blood pressure.

4.3 Protocol Violations:

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

1. Intubation of a treatment group infant in the DR for the exclusive purpose of giving surfactant, in the absence of bradycardia (HR< 100 bpm) and/or poor color or an SpO2< 85-90% in an infant with adequate spontaneous respirations or receiving adequate ventilation
2. Failure to continue CPAP on admission to the NICU for a treatment infant requiring supplemental oxygen
3. Intubation and surfactant administration of a treatment infant without meeting stated protocol criteria.
4. Failure to extubate a Treatment infant who fulfills all the extubation criteria.
5. Extubation of a Control infant who does not meet any of the Extubation criteria.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians and provide a written summary including steps taken to avoid future violations.

4.4 Adverse Events

Serious and unanticipated adverse events may be anticipated in this vulnerable population. Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)[61]
4. Death

These outcomes will be evaluated on a monthly basis by RTI, and if the incidence of any of these outcomes is determined to be 5% - 10% greater in any arm of the study, this information will be provided to the Study PI and committee and the DSMC for immediate consideration, and evaluated for consideration of termination of the study or treatment arm.

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 logistic regression analysis of the percent of each Group (Treatment vs Control, High vs Low SpO2) who developed their respective outcome measure (survival without BPD or ROP at 36 weeks respectively). An important analysis of a secondary outcome will determine if there is an effect of the interventions on the percent infants who survive without neurodevelopmental sequelae at 2 years For all secondary outcomes, univariate analysis for continuous variables will be performed using parametric (e.g., Student t tests, ANOVA), and non-parametric (e.g., Mann-Whitney U) tests where appropriate; categorical variables including the primary outcome, feasibility, will be examined by Chi square analysis. Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of, various factors, (e.g., birth weight, gestational age, gender, treatment group, center, etc.) upon secondary outcomes (i.e., time to improvement in oxygen saturation, duration of positive pressure ventilation, five minute Apgar score, duration of mechanical ventilation, surfactant requirement, incidence of air leaks, and incidence of BPD).

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP. Mortality or NDI is a secondary outcome. For the cohort of infants born in 2000, 401-1000g birth weight, we have the following prevalence of outcomes for four subgroups of that cohort: Please note that we used population groupings to include or exclude infants of 23 and 28 weeks. These additional groups do not change the sample size estimates as the outcomes are essentially similar.

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI

23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

If the study is powered for the two outcomes, Death/BPD and Death/>Stage III ROP, then the sample size is driven by the prevalence nearest 50% for a given absolute percentage detectable change in the outcome. In this case it's the Death/>Stage III ROP outcome with a range of 44.5% to 53.1% across the subgroups. Furthermore, the sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Hence, for any of the four groups the table below gives the total sample sizes required for a range of absolute percent changes, a two-tailed alpha level test of 5% and for powers of 80% and 90%. The N1 column powers the 2 x 2 factorial for the two primary outcomes and the N2 column assures comparable power for the Death/NDI outcome.

With regard to the power for detecting the interaction between the two factors in the factorial, a fourfold increase in the stated sample size would be required to detect an interaction effect as large or larger as that stated in the table (i.e. the Detectable Difference), assuming the same alpha level and power. The interaction effect referred to is the classical one where the difference in outcome for one of the treatments in the factorial differs according to the level of the other treatment (i.e. the treatment effects are not additive).

If the study is powered for the two primary outcomes and mortality/NDI is considered as a secondary outcome then the table below gives the total sample size required for a 5% overall level test at 80% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance and a conservative outcome rate of 50% in making the calculations. These sample sizes are given in the N1 column and would also allow a 10% difference in NDI/death to be detected with a power of 73%. If an 80% power is desired for the NDI/mortality outcome this would result in sample sizes in the N2 column.

TOTAL SAMPLE SIZES REQUIRED

	80% Power		90% Power	
Detectable Difference (absolute %)	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208

13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

* sample sizes to insure the appropriate power for the two primary outcomes (BPD/Death, ROP/Death)

** sample sizes to insure the appropriate power for the secondary outcome (NDI/Death)

We have increased the sample size by a factor of 1.12 to allow for multiples to be randomized to the same treatment as this introduces a clustering effect into the design. The analysis of the GDB data base resulted in the 1.12 estimate. We also inflated the sample sizes by 17% to adjust for attrition after discharge and before follow-up. This figure was also determined from the GDB data base.. Thus the actual sample size for this trial would be 1310 for 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. This sample size is not sufficient to permit detection of interactive effects between the two treatments with reasonable power.

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

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

--BPD/Mortality—67%
--ROP ≥ Grade III/Mortality—47%
--NDI/Mortality—61%.

Sample sizes were calculated for a range of absolute treatment effects and 10% seemed to be the smallest plausible effect for the study. Rounding the above rates to 65, 45, and 60 percent the following tables show what the data would look like under the assumption of a 10% reduction in outcome and control rates of 65, 45, and 60 percent for the DRCPAP (No)/ SpO2 (High) group. Interactive effects are assumed to be zero. Tables are presented which show treatment effects when both treatments affect the BPD and the ROP outcomes and when only one of the treatments affects outcome. The NDI table is only for the case where both treatments affect outcome.

Table IA

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

		SpO2		
		Low	High	Overall
CPAP	Yes	45	55	50
	No	55	65	60
	Overall	50	60	55

Table IB

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

		SpO2		
		Low	High	Overall
CPAP	Yes	55	55	55
	No	65	65	65
	Overall	60	60	60

Table IIA

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

SpO2

		SpO2		
		Low	High	Overall
CPAP	Yes	25	35	30
	No	35	45	40
	Overall	30	40	35

Table IIB

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

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

Table III

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

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

9.1 Quality Control

The selection of personnel will be left to the site PI's. No specific job descriptions are required for this protocol. The actual duties of the individual who will perform the randomization will be detailed in the manual for the study. Protocol violations will be reviewed, and if frequent,

may require a site visit and consideration for termination of a collaborating site.

10.1 Risks and Benefits

Potential risks to the use of CPAP and/or PEEP include pneumothoraces; however this is unlikely to be increased over the risk of PPV alone. The level of CPAP/PEEP will be set at 5-6 cmH_2O, a level that is not thought to increase the incidence of pneumothorax. Recent data from Dr Morley suggest that this level is probably the lowest effective level especially when the infant's mouth is open, and is well tolerated. Objections to use of PEEP or CPAP could be countered by the argument that the majority of neonatologists use PEEP in resuscitation, thus the standard of care at most centers probably include the administration of CPAP and/or PEEP. Another potential risk is the administration of CPAP in the DR to infants without respiratory distress, which could conceivably cause vagal stimulation and resultant bradycardia and gastric distension.

Perhaps the major risk of this trial is that the known benefit of early surfactant with a reduction of death and disease severity, and a reduction of BPD with natural surfactant may not be offset by the early use of CPAP. However, the increasing trend in the use of early CPAP without such evidence represents an even greater risk.

Appendix A

Study Tables

Table 1. Patient Description

	Treatment	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min < 3 Assigned			
Apgar 5 min < 3 Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Treatment	Control	P Value
Total Duration of Mechanical Vent (M +SD)			
Duration of Oxygen (Total days)			
Duration of CPAP			
Duration of nSIMV			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, %)			
Other air leaks (N, %)			
BPD at 36 weeks (O_2 dependence)			
BPD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %)			
Number receiving PNS for BPD (N, % %)			
Alive without neurdevelopmental impairment at (18-22 months) years (N, %, +/-SD)			

Appendix B

Study Tables

Table 1. Patient Description

	Low Saturation	High Saturation	RR	CI	p value
Birth weight (grams) (M + SD)					
Gestation (weeks) (M + SD)					
Race (W, B, H, other) %					
Antenatal steroids (%)					
Apgars ≤3 at 5 min					

Table 2. Primary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Threshold ROP/Surgery or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					
BPD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
BPD in alive infants at 36 weeks (%)					
IVH 3 or 4/PVL or death by 36 weeks (%)					
IVH 3 or 4 in alive infants at 36 weeks (%)†					
Cystic PVL in alive infants at 36 weeks (%)†					
Neurodevelopmental impairment or death by 18-22 months (%)					
Death by 18-22 months (%)					
Neurodevelopmental impairment at 18-22 months (%)†					
Cerebral palsy at 18-22 months (%)†					
MDI < 70 (%)					
PDI < 70 (%)					
Any blindness at 18-22 months (%)†					
Unilateral blindness at 18-22 months (%)†					
Deafness at 18-22 months†					

†Analyzed for survivors

Table 4. Other Outcomes

	Low Saturation	High Saturation	RR CI	P Value
Total Duration of Ventilation (M+SD)				
On ventilator or death by day 7 (%)				
Pneumothorax (%)				
Any air leak (%)				
Postnatal steroids for BPD (%)				
Necrotizing enterocolitis ≥2 (%)				
PDA requiring surgery				

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	**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 Blackmon, Lillian; Bell, Edward; Engle, William, and et al. Postnatal coricosteroids to treat or prevent chronic lung disease in preterm infants. 2002 Feb; 109, (2): 330-7

61 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: Diane Timmer
To: Vivek Narendran
Cc: Edward Donovan; Higgins, Rosemary (NIH/NICHD); nfiner@ucsd.edu
Subject: Re: SUPPORT conf call
Date: Wednesday, July 14, 2004 9:28:40 AM

Vivek -

To join the call:

Dial Tollfree: 866-675(b) (6)
Passcode: (b) (6) (# when prompted)

Diane

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

>>> Edward Donovan 07/14/04 08:53AM >>>

Vivek,
Thanks.
I'll ask Diane to send you the details.
And I'll let Neil Finer and Rose Higgins know that you will be attending the SUPPORT conference call on stopping rules for me.
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

>>> Vivek Narendran 07/13/2004 6:19:19 PM >>>
Sure. I am free that afternoon. Please send me the details.
Vivek

Vivek Narendran MD, MRCP (UK)
Assistant Professor
Division of Neonatology
Cincinnati Children's Hospital
Cincinnati, Ohio 45229
Tel: 513-558-0557
Fax: 513-558-7770
>>> Edward Donovan 07/13/04 1:58 PM >>>
Vivek,

Can you be on a conference call Monday July 19 at 1pm to discuss stopping rules for the SUPPORT trial?
I have a conflict.
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:	Petrie, Carolyn
To:	"Neil Finer"; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; sduara@miaml.edu; edward.donovan@chmcc.org; wcarlo@peds.uab.edu; aaf2@cwru.edu; Ruth Everett (reverett@med.miaml.edu); wrich@ucsd.edu
Cc:	Hastings, Betty J.; Das, Abhik; Petrie, Carolyn; Diane Timmer (Cincinnati) (diane.timmer@cchmc.org); Heidi Squibb (UCSD) (hsquibb@ucsd.edu); Marsha Sumner (UAB) (msumner@peds.uab.edu); (mlg@cwru.edu)
Subject:	SUPPORT Conf call - Mon July 19, 1pm EDT (10am PDT)
Date:	Monday, June 28, 2004 4:44:47 PM

The SUPPORT conference call to discuss stopping rules for this trial is scheduled for
Monday July 19
1:00 PM ET (10:00 AM PT)

To join the call:
Dial Tollfree: **866-675-**(b) (6)
Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Carolyn Petrie

Neonatal Research Network Coordinator
RTI International
6110 Executive Blvd
Suite 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"; "Michele"
Subject: RE: SUPPORT Trial
Date: Friday, June 25, 2004 10:18:57 AM

Wally
What about 1:00 PM Eastern Monday July 19? Can the rest of us do this date so that Wally can participate?
Thanks
Neil
Neil

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, June 25, 2004 7:11 AM
To: Neil Finer; Higgins, Rosemary (NIH/NICHD)
Cc: Wally Carlo, M.D.; bkh@rti.org; wrich@ucsd.edu; sduara@miami.edu; edward.donovan@cchmc.org; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Subject: RE: SUPPORT Trial

July 15 is a really bad day for me because we have our annual conference for which I am committed the whole day because I am the organizer. I am available every day in July before 10 Eastern and after 12 Eastern, as I am on service in July.

Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, June 24, 2004 11:04 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Wally Carlo, M.D.; nfiner@ucsd.edu; bkh@rti.org; wrich@ucsd.edu; sduara@miami.edu; edward.donovan@cchmc.org; aaf2@po.cwru.edu; mcw3@po.cwru.edu
Subject: Re: SUPPORT Trial

Rose
I will be away for the next 2 weeks. Can everyone look at the possibility of a call on Thursday July 15th at 11-:00 AM Eastern 8:00 AM Pacific. I can make the call as late as 4:00 PM Eastern Please let me and Rose know if this date will work Thanks
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <wcarlo@peds.uab.edu>; <nfiner@ucsd.edu>; <bkh@rti.org>; <wrich@ucsd.edu>; <sduara@miami.edu>; <edward.donovan@cchmc.org>; <aaf2@po.cwru.edu>; <mcw3@po.cwru.edu>
Cc: <poo@rti.org>
Sent: Thursday, June 24, 2004 6:34 PM
Subject: Re: SUPPORT Trial

> Ken can help us with this - initial stopping rule should dictate a stringent
> p value (less than 0.001)
>
> How about we set up a call with the subcommittee to discuss?

> Rose
> ----------
> Sent from my BlackBerry Wireless Handheld
>
>
> -----Original Message-----
> From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> To: Neil Finer <nfiner@ucsd.edu>; Hastings, Betty J. <bkh@rti.org>; Higgins,
> Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Wade Rich
> <wrich@ucsd.edu>; Shahnaz Duara <sduara@miami.edu>; Ed Donovan
> <Edward.Donovan@cchmc.org>; Avroy A. Fanaroff, M.D.
> <aaf2@po.cwru.edu>; Michele Walsh-Sukys <mcw3@po.cwru.edu>
> CC: Poole, W. Kenneth <poo@rti.org>
> Sent: Thu Jun 24 20:58:29 2004
> Subject: RE: SUPPORT Trial
>
> Neil: We should be careful with stopping rules and early in the trial, when
> the # is small there can be large diferences in outcomes that do not
> persist. Wally
>
> _____
>
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wed 6/23/2004 2:15 AM
> To: Hastings, Betty J.; Rose Higgins; Wade Rich; Neil Finer; Wally
> Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.;
> Michele Walsh-Sukys
> Cc: Poole, W. Kenneth
> Subject: SUPPORT Trial
>
>
> Hello All
> I made a few more corrections to the protocol. I would like you to review.
> Betty will make all subsequent official drafts and the eventual final
> version.
> I think that we should think about stopping rules for this study. We
> have introduced as a safety issue that we measure 4 outcomes - air
> leak including
> PIE, compressions and/or the use of Code medications - adrenaline in
> the NICU, death, ivh grade 3 or 4. Should we be thinking about what
> difference in these parameters would lead us to stop the trial - a
> 5-10% increase in any of these in the CPAP vs Control etc? Would this
> be done by a sequential
> analysis as the study is conducted as a continuous safety issue?
> Please look
> carefully at the Postnatal steroid section in Section 4.2 and the
> Adverse outcome etc in Section 4.4. My changes are in Blue with yellow highlight.
> I'm not sure what to postulate as safety for the pulse oximeter arm although
> hypoxic injury could be a problem probably offset by ROP. We could
> look at measures of oxygen injury - ie MDA - and measure at birth and
> 1 week and at

> 4 weeks. I will develop a Secondary for this.
> We should officially vote on the Hintz protocol. I would like to see
> this move ahead with the DTI as an Ancillary. If you can let me and
> Rose know whether you approve the Hintz MRI protocol including MR but not DTI.
> If we approve. Rose can then get the approval of the Steering
> Committee for
> this study and try to find the necessary funding.
> Lets try to complete the Pilots ASAP. I think that at least 4 of our centers
> should be able to enroll patients in the definitive trial within 3 months.
I
> think that we ought to take the current version to our respective IRBs.
> We should also prioritize the other Secondaries. You have seen them
> all except the Cotton Surfactant protocol which I have attached. I
> have asked Dale to review the Inositol protocol. She will be away for
> 2 weeks. I have
> reattached Carmen Herrera's protocol as well. I think that we have
> agreed that this protocol is probably too close to the SUPPORT design,

> but in your
> spare time relook at it. We need to be fair and recognize the work she

> has done. From my discussions with everyone, I get the impression that

> the pulmonary follow-up may be a reasonable study, but very time consuming.
> I will suggest a Rank order
> 1. Hintz
> 2. Asthma Genes
> 3. The others as a group
> I will ask Shahnaz for written comments on the Genomics protocols -
> Asthma Genes, Surfactant, Inositol.
> Look forward to your responses and the vote re the Hintz protocol.
> Good to see you at the meeting.
> Ed, I hope you were having fun!! We kept them entertained!!
> Be well
> Neil
>

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Friday, June 25, 2004 9:05:57 AM

As I indicated earlier, I think the stopping rules for efficacy should be different than those for AEs.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 24, 2004 9:34 PM
To: 'wcarlo@peds.uab.edu'; 'nfiner@ucsd.edu'; 'bkh@rti.org'; 'wrich@ucsd.edu'; 'sduara@miami.edu'; 'edward.donovan@cchmc.org'; 'aaf2@po.cwru.edu'; 'mcw3@po.cwru.edu'
Cc: 'poo@rti.org'
Subject: Re: SUPPORT Trial

Ken can help us with this - initial stopping rule should dictate a stringent p value (less than 0.001)

How about we set up a call with the subcommittee to discuss? Rose

---

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Neil Finer <nfiner@ucsd.edu>; Hastings, Betty J. <bkh@rti.org>; Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Wade Rich <wrich@ucsd.edu>; Shahnaz Duara <sduara@miami.edu>; Ed Donovan <Edward.Donovan@cchmc.org>; Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>; Michele Walsh-Sukys <mcw3@po.cwru.edu>
CC: Poole, W. Kenneth <poo@rti.org>
Sent: Thu Jun 24 20:58:29 2004
Subject: RE: SUPPORT Trial

Neil: We should be careful with stopping rules and early in the trial, when the # is small there can be large diferences in outcomes that do not persist. Wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wed 6/23/2004 2:15 AM
To: Hastings, Betty J.; Rose Higgins; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Cc: Poole, W. Kenneth
Subject: SUPPORT Trial

Hello All
I made a few more corrections to the protocol. I would like you to review. Betty will make all subsequent official drafts and the eventual final version.
I think that we should think about stopping rules for this study. We have introduced as a safety issue that we measure 4 outcomes - air leak including

PIE, compressions and/or the use of Code medications - adrenaline in the NICU, death, ivh grade 3 or 4. Should we be thinking about what difference in these parameters would lead us to stop the trial - a 5-10% increase in any of these in the CPAP vs Control etc? Would this be done by a sequential analysis as the study is conducted as a continuous safety issue? Please look carefully at the Postnatal steroid section in Section 4.2 and the Adverse outcome etc in Section 4.4. My changes are in Blue with yellow highlight. I'm not sure what to postulate as safety for the pulse oximeter arm although hypoxic injury could be a problem probably offset by ROP. We could look at measures of oxygen injury - ie MDA - and measure at birth and 1 week and at 4 weeks. I will develop a Secondary for this.
We should officially vote on the Hintz protocol. I would like to see this move ahead with the DTI as an Ancillary. If you can let me and Rose know whether you approve the Hintz MRI protocol including MR but not DTI. If we approve. Rose can then get the approval of the Steering Committee for this study and try to find the necessary funding. Lets try to complete the Pilots ASAP. I think that at least 4 of our centers should be able to enroll patients in the definitive trial within 3 months. I think that we ought to take the current version to our respective IRBs. We should also prioritize the other Secondaries. You have seen them all except the Cotton Surfactant protocol which I have attached. I have asked Dale to review the Inositol protocol. She will be away for 2 weeks. I have reattached Carmen Herrera's protocol as well. I think that we have agreed that this protocol is probably too close to the SUPPORT design, but in your spare time relook at it. We need to be fair and recognize the work she has done. From my discussions with everyone, I get the impression that the pulmonary follow-up may be a reasonable study, but very time consuming. I will suggest a Rank order 1. Hintz 2. Asthma Genes 3. The others as a group
I will ask Shahnaz for written comments on the Genomics protocols - Asthma Genes, Surfactant, Inositol. Look forward to your responses and the vote re the Hintz protocol. Good to see you at the meeting. Ed, I hope you were having fun!! We kept them entertained!! Be well Neil

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Friday, June 25, 2004 8:09:30 AM

Subcommittee only? Just want to double check.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, June 25, 2004 7:13 AM
To: 'petrie@rti.org'
Subject: Fw: SUPPORT Trial

Can you see if this will work?

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Neil Finer <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
CC: wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; bkh@rti.org <bkh@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>; sduara@miami.edu <sduara@miami.edu>; edward.donovan@cchmc.org <edward.donovan@cchmc.org>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; mcw3@po.cwru.edu <mcw3@po.cwru.edu>
Sent: Fri Jun 25 00:03:58 2004
Subject: Re: SUPPORT Trial

Rose
I will be away for the next 2 weeks. Can everyone look at the possibility of a call on Thursday July 15th at 11-:00 AM Eastern 8:00 AM Pacific. I can make the call as late as 4:00 PM Eastern
Please let me and Rose know if this date will work
Thanks
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: <wcarlo@peds.uab.edu>; <nfiner@ucsd.edu>; <bkh@rti.org>; <wrich@ucsd.edu>; <sduara@miami.edu>; <edward.donovan@cchmc.org>; <aaf2@po.cwru.edu>; <mcw3@po.cwru.edu>
Cc: <poo@rti.org>
Sent: Thursday, June 24, 2004 6:34 PM
Subject: Re: SUPPORT Trial

> Ken can help us with this - initial stopping rule should dictate a stringent
> p value (less than 0.001)
>
> How about we set up a call with the subcommittee to discuss?
> Rose
> ---
> Sent from my BlackBerry Wireless Handheld
>
>
> -----Original Message-----
> From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> To: Neil Finer <nfiner@ucsd.edu>; Hastings, Betty J. <bkh@rti.org>;

Higgins,
> Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Wade Rich <wrich@ucsd.edu>;
> Shahnaz Duara <sduara@miami.edu>; Ed Donovan <Edward.Donovan@cchmc.org>;
> Avroy A. Fanaroff, M.D. <aaf2@po.cwru.edu>; Michele Walsh-Sukys
> <mcw3@po.cwru.edu>
> CC: Poole, W. Kenneth <poo@rti.org>
> Sent: Thu Jun 24 20:58:29 2004
> Subject: RE: SUPPORT Trial
>
> Neil: We should be careful with stopping rules and early in the trial,
when
> the # is small there can be large diferences in outcomes that do not
> persist. Wally
>
> _____
>
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wed 6/23/2004 2:15 AM
> To: Hastings, Betty J.; Rose Higgins; Wade Rich; Neil Finer; Wally Carlo,
> M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele
> Walsh-Sukys
> Cc: Poole, W. Kenneth
> Subject: SUPPORT Trial
>
>
> Hello All
> I made a few more corrections to the protocol. I would like you to review.
> Betty will make all subsequent official drafts and the eventual final
> version.
> I think that we should think about stopping rules for this study. We have
> introduced as a safety issue that we measure 4 outcomes - air leak
including
> PIE, compressions and/or the use of Code medications - adrenaline in the
> NICU, death, ivh grade 3 or 4. Should we be thinking about what difference
> in these parameters would lead us to stop the trial - a 5-10% increase in
> any of these in the CPAP vs Control etc? Would this be done by a
sequential
> analysis as the study is conducted as a continuous safety issue? Please
look
> carefully at the Postnatal steroid section in Section 4.2 and the Adverse
> outcome etc in Section 4.4. My changes are in Blue with yellow highlight.
> I'm not sure what to postulate as safety for the pulse oximeter arm
although
> hypoxic injury could be a problem probably offset by ROP. We could look at
> measures of oxygen injury - ie MDA - and measure at birth and 1 week and
at
> 4 weeks. I will develop a Secondary for this.
> We should officially vote on the Hintz protocol. I would like to see this
> move ahead with the DTI as an Ancillary. If you can let me and Rose know
> whether you approve the Hintz MRI protocol including MR but not DTI.
> If we approve. Rose can then get the approval of the Steering Committee
for
> this study and try to find the necessary funding.
> Lets try to complete the Pilots ASAP. I think that at least 4 of our
centers
> should be able to enroll patients in the definitive trial within 3 months.
I
> think that we ought to take the current version to our respective IRBs.
> We should also prioritize the other Secondaries. You have seen them all
> except the Cotton Surfactant protocol which I have attached. I have asked

> Dale to review the Inositol protocol. She will be away for 2 weeks. I have
> reattached Carmen Herrera's protocol as well. I think that we have agreed
> that this protocol is probably too close to the SUPPORT design, but in your
> spare time relook at it. We need to be fair and recognize the work she has
> done. From my discussions with everyone, I get the impression that the
> pulmonary follow-up may be a reasonable study, but very time consuming.
> I will suggest a Rank order
> 1. Hintz
> 2. Asthma Genes
> 3. The others as a group
> I will ask Shahnaz for written comments on the Genomics protocols - Asthma
> Genes, Surfactant, Inositol.
> Look forward to your responses and the vote re the Hintz protocol.
> Good to see you at the meeting.
> Ed, I hope you were having fun!! We kept them entertained!!
> Be well
> Neil
>

From: Neil Finer
To: Wally Carlo, M.D.; Hastings, Betty J.; Higgins, Rosemary (NIH/NICHD); Wade Rich; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Cc: Poole, W. Kenneth
Subject: Re: SUPPORT Trial
Date: Friday, June 25, 2004 12:05:49 AM

I agree. I would like us to at least have discussed this issue before we start the trial. I will try to set up a call in mid July.
Be well
Neil

----- Original Message -----
From: Wally Carlo, M.D.
To: Neil Finer ; Hastings, Betty J. ; Rose Higgins ; Wade Rich ; Shahnaz Duara ; Ed Donovan ; Avroy A. Fanaroff, M.D. ; Michele Walsh-Sukys
Cc: Poole, W. Kenneth
Sent: Thursday, June 24, 2004 5:58 PM
Subject: RE: SUPPORT Trial

Neil: We should be careful with stopping rules and early in the trial, when the # is small there can be large diferences in outcomes that do not persist. Wally

---

From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wed 6/23/2004 2:15 AM
To: Hastings, Betty J.; Rose Higgins; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-Sukys
Cc: Poole, W. Kenneth
Subject: SUPPORT Trial

Hello All
I made a few more corrections to the protocol. I would like you to review. Betty will make all subsequent official drafts and the eventual final version.
I think that we should think about stopping rules for this study. We have introduced as a safety issue that we measure 4 outcomes - air leak including PIE, compressions and/or the use of Code medications - adrenaline in the NICU, death, ivh grade 3 or 4. Should we be thinking about what difference in these parameters would lead us to stop the trial - a 5-10% increase in any of these in the CPAP vs Control etc? Would this be done by a sequential analysis as the study is conducted as a continuous safety issue? Please look carefully at the Postnatal steroid section in Section 4.2 and the Adverse outcome etc in Section 4.4. My changes are in Blue with yellow highlight.
I'm not sure what to postulate as safety for the pulse oximeter arm although hypoxic injury could be a problem probably offset by ROP. We could look at measures of oxygen injury - ie MDA - and measure at birth and 1 week and at 4 weeks. I will develop a Secondary for this.
We should officially vote on the Hintz protocol. I would like to see this move ahead with the DTI as an Ancillary. If you can let me and Rose know whether you approve the Hintz MRI protocol including MR but not DTI.
If we approve. Rose can then get the approval of the Steering Committee for this study and try to find the necessary funding.
Lets try to complete the Pilots ASAP. I think that at least 4 of our centers should be able to enroll patients in the definitive trial within 3 months. I think that we ought to take the current version to our respective IRBs.
We should also prioritize the other Secondaries. You have seen them all except the Cotton Surfactant protocol which I have attached. I have asked Dale to review the Inositol protocol. She will be away for 2 weeks. I have reattached Carmen Herrera's protocol as well. I think that we have agreed that this protocol is probably too close to the SUPPORT design, but in your spare time relook

at it. We need to be fair and recognize the work she has done. From my discussions with everyone, I get the impression that the pulmonary follow-up may be a reasonable study, but very time consuming.
I will suggest a Rank order
1. Hintz
2. Asthma Genes
3. The others as a group
I will ask Shahnaz for written comments on the Genomics protocols - Asthma Genes, Surfactant, Inositol.
Look forward to your responses and the vote re the Hintz protocol.
Good to see you at the meeting.
Ed, I hope you were having fun!! We kept them entertained!!
Be well
Neil

From: Poole, W. Kenneth
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: SUPPORT Trial
Date: Thursday, June 24, 2004 9:33:37 AM

I don't know of any instance where the DSMC has set the stopping rules. I suggest we have rules similar to those for Phototherapy: look at efficacy four times equally spaced throughout enrollment and monitor AEs more frequently (e.g. after every 30 enrollees).

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, June 24, 2004 9:23 AM
To: 'Avroy A. Fanaroff'; bkh@rti.org; wrich@ucsd.edu; nfiner@ucsd.edu; WCarlo@PEDS.UAB.EDU; sduara@miami.edu; Edward.Donovan@cchmc.org; mcw3@po.cwru.edu
Cc: poo@rti.org; Alan Jobe (E-mail)
Subject: RE: SUPPORT Trial

The DSMC will discuss the stopping rules, but we need to provide some guidance, especially since we have had so many long and arduous conversations with the group about where the difficulties lie. Please think about specific issues at your site so they can be somehow integrated into the input we give the DSMC.
Thanks
Rose

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Wednesday, June 23, 2004 9:15 AM
To: bkh@rti.org; Higgins, Rosemary (NIH/NICHD); wrich@ucsd.edu; nfiner@ucsd.edu; WCarlo@PEDS.UAB.EDU; sduara@miami.edu; Edward.Donovan@cchmc.org; mcw3@po.cwru.edu; nfiner@ucsd.edu
Cc: poo@rti.org
Subject: Re: SUPPORT Trial

Hi
Thanks for all your hard work on this protocol
Neil your energy never ceases to amaze me, but you are shredding trees every week with all the modifications to the protocol
I have enough versions to fill a file cabinet
Isn't it the duty and responsibility of the DSMC to determine the stopping criteria?
We can advise them, but I believe that they need to discuss it.
Regards
Av

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

From: Neil Finer
Date: 06/23/04 03:16:48
To: Hastings, Betty J.; Rose Higgins; Wade Rich; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; Avroy A. Fanaroff, M.D.; Michele Walsh-

Sukys
Cc: Poole, W. Kenneth
Subject: SUPPORT Trial

Hello All
I made a few more corrections to the protocol. I would like you to review. Betty will make all subsequent official drafts and the eventual final version.
I think that we should think about stopping rules for this study. We have introduced as a safety issue that we measure 4 outcomes - air leak including PIE, compressions and/or the use of Code medications - adrenaline in the NICU, death, ivh grade 3 or 4. Should we be thinking about what difference in these parameters would lead us to stop the trial - a 5-10% increase in any of these in the CPAP vs Control etc? Would this be done by a sequential analysis as the study is conducted as a continuous safety issue? Please look carefully at the Postnatal steroid section in Section 4.2 and the Adverse outcome etc in Section 4.4. My changes are in Blue with yellow highlight.
I'm not sure what to postulate as safety for the pulse oximeter arm although hypoxic injury could be a problem probably offset by ROP. We could look at measures of oxygen injury - ie MDA - and measure at birth and 1 week and at 4 weeks. I will develop a Secondary for this.
We should officially vote on the Hintz protocol. I would like to see this move ahead with the DTI as an Ancillary. If you can let me and Rose know whether you approve the Hintz MRI protocol including MR but not DTI.
If we approve. Rose can then get the approval of the Steering Committee for this study and try to find the necessary funding.
Lets try to complete the Pilots ASAP. I think that at least 4 of our centers should be able to enroll patients in the definitive trial within 3 months. I think that we ought to take the current version to our respective IRBs.
We should also prioritize the other Secondaries. You have seen them all except the Cotton Surfactant protocol which I have attached. I have asked Dale to review the Inositol protocol. She will be away for 2 weeks. I have reattached Carmen Herrera's protocol as well. I think that we have agreed that this protocol is probably too close to the SUPPORT design, but in your spare time relook at it. We need to be fair and recognize the work she has done. From my discussions with everyone, I get the impression that the pulmonary follow-up may be a reasonable study, but very time consuming.
I will suggest a Rank order
1. Hintz
2. Asthma Genes
3. The others as a group
I will ask Shahnaz for written comments on the Genomics protocols - Asthma Genes, Surfactant, Inositol.
Look forward to your responses and the vote re the Hintz protocol.
Good to see you at the meeting.
Ed, I hope you were having fun!! We kept them entertained!!
Be well
Neil

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

MORBIDITY AND MORTALITY ASSOCIATED WITH EXTUBATION FAILURE IN EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANTS

A. ABSTRACT

Objective: To determine if extubation failure increases the risk of neonatal morbidity, including bronchopulmonary dysplasia (BPD), and mortality in ELBW infants.

Methods: Infants with a gestational age from 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate enrolled in both the SUPPORT (SUrfactant Positive Airway Pressure and Pulse Oximetry) Trial in ELBW Infants and the NICHD Neonatal Research Network Database will be included in a prospective cohort analysis of the impact of extubation failure on subsequent morbidities, including BPD, and mortality. Infants in the first 28 days of life will be grouped based on the outcome of the initial extubation attempt as either extubation success or failure. Cases (extubation failures) will be compared with Controls (successful extubation) for the risk of the composite outcome death or BPD at 36 weeks PCA, BPD (BPD determined by Physiologic Definition), death, late-onset sepsis/bacteremia (defined as positive blood culture and/or antibiotics for ≥ 5 days after 72 hours of life), prolonged hospital stay (> 120 days [PHS] or > 40 weeks post-menstrual age [40wPHS]), threshold retinopathy of prematurity (ROP)/surgery, necrotizing enterocolitis (NEC [medical or surgical]), days to achieve full enteral feeds, and days to regain birth weight.

B. Statement of the Problem

Prolonged mechanical ventilation for more than 7 days has a synergistic effect with antenatal infection and it is associated with a significant increased risk for the development of BPD among surviving preterm infants (1). In addition, mechanical ventilation has been associated with respiratory muscle atrophy and inhibition, even elimination, of the respiratory motor output (2).

An increased mortality exceeding 40% was found both in medical (3, 4) and general surgical adult ICU patients who needed reintubation (5). After adjusting for severity of illness and comorbid conditions, reintubation after planned extubation had a significant independent association with increased risk for prolonged ICU stay (4, 6), nosocomial pneumonia, and tracheostomy (6). Two pediatric trials (7, 8) reveal higher mortality in children who fail extubation compared to those who do not. In the Farias et al. study (7), the in-unit mortality and the in-hospital mortality were significantly higher among children who required reintubation when compared with successfully extubated patients (in-unit mortality: 39.3 versus 2.9%; in-hospital mortality: 46.4 versus 6.3%). The Kuracheck et al. data (8) were consistent with these results showing higher mortality rate in patients failing extubation (4% versus 0.8%; $p<0.01$). There are no equivalent studies in neonates despite the fact that almost 40% of ELBW infants fail extubation (9).

C. Hypothesis

1. **Primary Hypothesis**: Infants who fail their initial extubation attempt have a higher risk of developing BPD or death compared to those who are successfully extubated.

2. Secondary Hypotheses:

a. Infants who fail their initial extubation attempt have a higher risk of developing BPD compared to those who are successfully extubated.

b. Infants who fail their initial extubation attempt have a higher risk of death compared to those who are successfully extubated.

c. Infants who fail their initial extubation attempt have a higher risk of developing late-onset sepsis/bacteremia compared to those who are successfully extubated.

d. Infants who fail their initial extubation attempt have a higher risk for prolonged hospital stay (PHS or 40wPHS) compared to those who are successfully extubated.

e. Infants who fail their initial extubation attempt have a higher risk of developing threshold ROP and require surgery for ROP compared to those who are successfully extubated.

f. Infants who fail their initial extubation attempt have a higher risk of developing NEC (medical or surgical) compared to those who are successfully extubated.

g. Infants who fail their initial extubation attempt have a higher risk of taking longer to achieve full enteral feeds compared to those who are successfully extubated.

h. Infants who fail their initial extubation attempt have a higher risk of taking longer to regain birth weight compared to those who are successfully extubated.

i. Infants who fail their initial extubation attempt have a higher risk of undergoing tracheostomy compared to those who are successfully extubated.

j. Infants who are extubated at ≤ 7 days of life have less risk of extubation failure compared to those who are extubated at > 7 days of life.

D. Specific Aims

a. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of BPD compared to those who are successful.

b. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of death compared to those who are successful.

c. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of late-onset sepsis/bacteremia compared to those who are successful.

d. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of prolonged hospital stay (PHS or 40wPHS) compared to those who are successful.

e. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of developing threshold ROP and require surgery for ROP compared to those who are successful.

f. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of NEC (medical or surgical) compared to those who are successful.

g. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of taking longer to achieve full enteral feeds compared to those who are successful.

h. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of taking longer to regain birth weight compared to those who are successful.

i. To determine if ELBW infants who fail their initial extubation attempt have a higher risk of undergoing tracheostomy compared to those who are successful.

j. To determine if the risk of extubation failure increases with prolonged mechanical ventilation (> 7 days) prior to the first extubation attempt in ELBW infants.

E. Rationale / justification

Extubation failure is associated with increased risk of death and morbidity in adults and older pediatric patients. Prolonged mechanical ventilation has a synergistic effect with antenatal infection and is associated with a significant increased risk for BPD in preterm infants. In addition, mechanical ventilation has been implicated in the development of respiratory muscle atrophy, an effect directly proportional to the duration of ventilatory support, and inhibition of the respiratory motor output. To date, no study has investigated the effects of extubation failure on BLD, sepsis, length of hospital stay, ROP, NEC, and mortality in infants who fail their initial extubation attempt compared to those who do not. There are no studies that assess the impact of the duration of mechanical ventilation on extubation outcome in ELBW infants.

F. Background / Previous Studies

Extubation failure is independently associated with increased risk of death after adjusting for severity of illness and comorbid conditions in both children and adults. Furthermore, reintubation after planned extubation has a significant independent association with increased risk for nosocomial pneumonia, tracheostomy, prolonged ICU stay, and transfer to long-term care or rehabilitation facility in adult patients. The improved survival of very premature infants has resulted in an increased number of them receiving prolonged mechanical ventilation. Prolonged mechanical ventilation has a synergistic effect with antenatal infection and is associated with a significant increased risk for CLD in preterm infants. Mechanical ventilation has been implicated in the development of respiratory muscle atrophy, an effect directly proportional to the duration of ventilatory support, and inhibition of the respiratory motor output. No study has assessed the effects of extubation failure on BPD, mortality, late-onset sepsis, length of hospital stay, ROP, NEC, time to achieve full enteral feeds, and time to regain birth weight in ELBW infants who fail their initial extubation attempt compared to those who are successful. Furthermore, there are no studies that assess the impact of the duration of mechanical ventilation prior to extubation on extubation outcome in ELBW infants.

G. Methods /Procedures

1) Study design: Prospective cohort study of infants enrolled both in the SUPPORT Trial of the NICHD Neonatal Research Network and in the NICHD Neonatal Network Database.

2) Definition of study population
    a. ELBW premature infants
        i. Inclusion criteria
            1. Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
            2. Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
            3. Infants whose parents/legal guardians have provided consent for enrollment
            4. Infants without known major congenital malformations
        ii. Exclusion criteria
            1. Any infant transported to the center after delivery
            2. Infants whose parents/legal guardians refuse consent
            3. Infants born during a time when the research apparatus/study personnel are not available.
            4. Infants < 24 weeks 0 days or ≥ 28 weeks 0 days, completed weeks of gestation

3) Description of study
- Intubation and extubation criteria are the same as those stated in the NICHD SUPPORT Trial protocol.
- Infants will be assigned to either one of two groups according to initial extubation outcome:
    i. Group 1: Failure of first extubation attempt (infant had to be reintubated, according to SUPPORT Trial protocol, within 7 days after initial extubation) occurring in the first 28 days of life
    ii. Group 2: Success of first extubation attempt (infant was not reintubated, according to SUPPORT Trial protocol, within 7 days after initial extubation) occurring in the first 28 days of life

4) Precise definition of primary/secondary outcomes
    a. Primary outcome: BPD or death
    b. Secondary outcomes:
        i. BPD
        ii. Death
        iii. Late-onset sepsis/bacteriemia
        iv. Length of hospital stay
        v. NEC (medical or surgical)
        vi. ROP/Threshold ROP/ROP surgery
        vii. Days to achieve full enteral feeds
        viii. Days to regain birth weight
    c. Descriptive measures
        i. Demographics
            1. Birth weight
            2. Gestational age
            3. SGA status
            4. Gender
            5. Race
    d. Predictors of Propensity Score for Extubation Failure (PSEF)
        i. Pregnancy complications
        ii. Prenatal steroids

iii. Prolonged rupture of membranes
iv. Maternal antibiotics
v. Apgar scores
vi. Delivery room resuscitation
    1. Oxygen
    2. Bag and mask ventilation
    3. Chest compressions
    4. Intubation
    5. Drugs (epinephrine, sodium bicarbonate, saline)
vii. Cord blood gas
viii. Admission
    1. Vital signs
        a. Temperature
        b. Blood pressure
        c. Glucose level
    2. Respiratory settings and blood gas
ix. Neonatal Therapeutic Intervention Score
x. Score for Neonatal Acute Physiology II (SNAP II ™)
xi. Pulmonary predictors (prior to extubation)
    1. Respiratory distress
        a. Oxygen requirement 6-24 hours
        b. Clinical RDS within 24 hours
        c. Need of respiratory support to age 24 hours
        d. Abnormal CXR within age 24 hours
    2. Surfactant (number of doses)
    3. Conventional ventilation
    4. High frequency ventilation
    5. Days of mechanical ventilation (conventional or high frequency) prior to extubation attempt
    6. Respiratory support (ventilator settings, oxygen requirement)
    7. Blood gas information
xii. Patent ductus arteriosus
xiii. Infection
    1. Intra-uterine infection
    2. Early onset septicemia/bacteremia prior to extubation
    3. Postnatal antibiotics prior to extubation
    4. Positive blood cultures prior to extubation
    5. Antibiotics at the time of extubation
xiv. Major surgery

5) Statistical analysis
    a. Data will be analyzed in aggregate and stratified by gestational age (2 strata, infants of 24 0/7ths to 25 0/7ths weeks, and 26 0/7ths to 27 6/7ths weeks) and by propensity scores (five strata)
    b. Continuous variables will be analyzed using two-tailed Student's *t* test if parametric and Mann-Whitney U test if non-parametric
    c. Categorical variables will be analyzed using Chi-square analysis
    d. Univariable and multivariable logistic regression analysis will be performed to determine the independent effect of extubation failure on BPD or death, BPD, death, late onset-sepsis, prolonged hospital stay, ROP, and NEC (medical or surgical), and the independent effect of mechanical ventilation duration on

extubation outcome (success/failure). A propensity score analysis will be used to better isolate the effect of extubation failure on death/BPD from the effect of characteristics of infants who are more likely to fail extubation (10, 11). Adjustments will also be made for birth weight, gestational age, chronologic age and PMA, respiratory support, and blood gas information at the time of extubation.

6) Sample size estimate
   1. Current estimates of outcome event rates
      a. The event rate for the primary outcome, BPD or death, is 48% for infants under 1000 grams birth weight (NICHD Network 2002 GDB, using the Physiologic Definition of BPD). The death rate for infants born weighing less than 1 Kg who survived the first 12 hours of life is 22% (NICHD Network 2000 and 2001).
      b. The reported average increase in mortality associated with extubation failure is approximately 25% (Table 1). There are no data equivalent to BPD in older children and adults.

TABLE 1.			MORTALITY		
Source	Population	% Extubation Failure	Extubation Failure	Extubation Success	p
Epstein 1997(4)	Medical ICU (adults)	15%	43%	12%	< 0.0001
Farias 2001(7)	PICU	18%	46.4%	6.3%	< 0.0001
Kurachek 2003(8)	PICU	6.2%	4%	0.8%	< 0.001

   2. Sample size

The tables below summarize the sample sizes required to detect four levels of absolute increase in death (Table 2) and in death or BPD (Table 3) for powers of 80, 85, and 90%. Calculations assume an alpha error of 0.05 and a two-sided test. N=number of total infants in both arms.

TABLE 2. DEATH			
% absolute increase	Power		
	80%	85%	90%
	N		
20% (22% to 42%)	170	194	226
15% (22% to 37%)	288	330	386
10% (22% to 32%)	618	706	826
5% (22% to 27%)	2322	2656	3106

TABLE 3. DEATH OR BPD			
% absolute increase	Power		
	80%	85%	90%
	N		
20% (48% to 68%)	190	216	252
15% (48% to 63%)	344	392	458
10% (48% to 58%)	780	892	1044
5% (48% to 53%)	3138	3588	4220

The logistic regression analysis will require at least ten extubation failure outcomes for every independent variable tested in the model.

7) Available population/compatibility with other ongoing protocols: not applicable

8) Estimate of projected recruitment time: same as NICHD Neonatal Network SUPPORT Trial

9) Risks/benefits

   a. Risks: Accidental disclosure of protected health information. Each infant enrolled in the NICHD Neonatal Network Database and the SUPPORT Trial is assigned a unique identifier with each site maintaining an identification log. Records outside the NICHD database will not be used. NICHD Neonatal Network database reports do not contain identifiable protected health information.

   b. Benefits: This study may show that extubation failure is independently associated with poor outcome and that it could serve as a marker of severity of illness in ELBW neonates. Alternatively, poor outcomes may be the cause of extubation failure; identifying patients at risk for poor outcomes after extubation failure and instituting alternative care practices could potentially reduce morbidity and mortality (4). This study may also show that prolonging mechanical ventilation negatively impacts on the infant's ability to be successfully extubated. Showing that prolonged mechanical ventilation increases the risk of extubation failure may prompt the neonatal community to be more aggressive in limiting the duration of mechanical ventilation thereby decreasing the risk of BPD and associated morbidities in ELBW infants.

REFERENCES

1. Van Marter LJ, Dammann O, Allred EN, et al. Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. *J Pediatr* 2002;140(2):171-6.

2. Dempsey JA, Skatrud JB. Apnea following mechanical ventilation may be caused by nonchemical neuromechanical influences. *Am J Respir Crit Care Med* 2001;163(6):1297-8.

3. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med* 1998;158(2):489-93.

4. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112(1):186-92.

5. Demling RH, Read T, Lind LJ, Flanagan HL. Incidence and morbidity of extubation failure in surgical intensive care patients. *Crit Care Med* 1988;16(6):573-7.

6. Dupont H, Le Port Y, Paugam-Burtz C, Mantz J, Desmonts M. Reintubation after planned extubation in surgical ICU patients: a case-control study. *Intensive Care Med* 2001;27(12):1875-80.

7. Farias JA, Retta A, Alia I, et al. A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. *Intensive Care Med* 2001;27(10):1649-54.

8. Kuracheck S NC, Quasney M, Rice T, Sachdeva R, Patel R et al. Extubation failure in pediatric intensive care:a multiple-center study of risk factors and outcomes. *Crit Care Med* 2003;31:2657-64.

9. Stefanescu B MP, Hansell B, Fuloria M, Morgan T, Aschner J. A randomized controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. *Pediatrics* 2003;112:1031-8.

10. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127(8 Pt 2):757-63.

11. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17(19):2265-81.

Secondary Study: Surfactant Protein Genetic Polymorphisms and Severity of RDS

CM Cotten

6.15.04

Study Question:

Are common genetic polymorphisms in surfactant protein A and B genes associated with severity of respiratory disease in extremely premature infants?

Statement of the Problem: The NICHD Neonatal Research Network will begin a prospective, randomized, factorial 2X2 design multi-center trial comparing 1) CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (< 30 minutes) surfactant and mechanical ventilation, and 2) maintentance 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 primary outcome measure for the CPAP/ventilation study will be survival without bronchopulmonary dysplasia (BPD) at 36 weeks, and the primary outcome for the SpO2 study will be a survival without occurrence of threshold ROP.

There is evidence that common genetic polymorphisms seen in surfactant protein alleles (> 1% of the population at large) are associated with increased risk of respiratory distress syndrome in infants. (Cole 2001, Hallman 2002) Previous studies of genetic associations with respiratory distress syndrome (RDS) have been hampered by inadequate sample size to allow for adequate multivariate analysis, especially in the smallest premature infants most at risk for respiratory distress syndrome, and have not looked at associations with subsequent pulmonary morbidity. (Kala 1998, Haataja 2000, Hallman 2002) In the future, if surfactant protein genetic variations are associated with pathophysiology of RDS and subsequent respiratory morbidity, a "severe RDS" phenotype, novel therapeutic regimens based on genotype could be developed.

The Network study offers an important opportunity to test significance of these polymorphisms in a large enough study population to adequately assess the risk of more severe respiratory disease attributable to surfactant protein genetic variation.

We propose that the Network add surfactant protein genetic polymorphism genotyping to the COT study to assess risk of death or BPD attributable to the polymorphisms.

Primary Hypotheses

We hypothesize that genetic polymorphisms in surfactant proteins A and B will have independent effects on risk of BPD or mortality in extremely premature infants.

Primary Outcome Variable
Survival without chronic lung disease; chronic lung disease defined by Network criteria of oxygen need at 36 weeks post conception or discharge home.

Secondary Hypotheses
We hypothesize surfactant protein genetic polymorphisms will have independent effects on other measures of neonatal outcome, especially those which could be associated with more severe RDS.

Secondary Outcome Variables

- Mortality/NDI at 18-22 months corrected age.
- Frequency of endotracheal intubation before 10 minutes of age
- Total duration of mechanical ventilation during the entire NICU stay
- Surfactant treatment doses
- Air leaks on admission and overall
- Duration of intubation
- Duration of mechanical ventilation
- Duration of oxygen supplementation
- Postnatal steroids to prevent or treat BPD
- Incidence of BPD at 36 weeks using the physiologic definition of BPD

Background
Respiratory Distress Syndrome is a complex disease involving multiple systems and influenced by multiple factors including gestational age, gender, and race. (Farrell 1976) Very early work in the field suggested an epidemiologic basis to suspect a genetic contribution to susceptibility to RDS. (Lakenau 1976) Cole et al, and Hallman et al, have summarized the evidence for the importance of genetic interaction with environmental influences in susceptibility of RDS, with discussion of the particular surfactant protein genotypes which appear to contribute to risk and severity of RDS (Cole 2001, Hallman 2002)

Current research suggests there are approximately 35,000 genes in the human genome, and three billion nucleotide base pairs. Experts estimate allelic heterogeneity in one of every 200 – 500 base pairs. Such variations occurring in at least one percent of the population are called single nucleotide polymorphisms or "SNP's". Much of this variation will have minimal impact on human disease, but some of this variation is likely responsible for genetic predispositions to complex, multifactorial disease. Previous associations have been found between SNP's and complex diseases such as Parkinson's Disease, Alzheimer's disease, and other diseases at the opposite extreme of life than ELBW infants. (Scott 2001, Pericak-Vance 2000)

SNP's have been discovered for genes coding for surfactant proteins. Previous investigations have found links between these SNP's and risk for other lung disease. Rather than mutations that are virtually incompatible with survival,

(Nogee 1993) these surfactant protein SNP's contribute to risk of disease that current therapy grants a reasonable chance for survival, but may be associated with higher risk of respiratory morbidities in premature infants. Evolution of detection methods and better understanding of these SNP's and their contribution to risk of more severe RDS and chronic lung disease will lead to new strategies of prevention and treatment, and may also be important considerations as covariates in clinical trials of respiratory interventions.

Candidate Genes for Analysis

SP-A: is a collagen-type (C-type) lectin, (collectin) like surfactant protein D and mannose-binding lectin, whose functions include the innate immune function of binding to various pathogen-associated molecular patterns as well as stabilizing intra-alveolar surfactant complexes. SP-A is essential to tubular myelin formation, and quantitation of SP-A predicts RDS risk in unborn fetuses. Low levels of SP-A at birth are associated with severe RDS and later chronic lung disease. (Hallman 1991) In a mouse model, complete lack of SP-A gene expression has been associated with susceptibility to respiratory infections rather than respiratory failure at birth. (Hallman 1988, Hallman 2002)

SP-A is coded by two closely-linked, highly homologous genes, (SP-A1 and SP-A2), each with 4 exons spanning about 5 kilobases, in chromosome 10q22-q23. Both genes are highly polymorphic. The SP-A alleles, that are actually intragenic haplotypes, have been denoted as $6A^n$ for the SP-A1 gene and $1A^n$ for the SP-A2 gene. Four SP-A1 alleles and five SP-A2 alleles occur with moderate frequency. An 11 base pair sequence is present in the 3' untranslated region of the major SP-A1 allele $6A^2$, and in all the SP-A2 alleles. (Hallman 2002, Cole 2001)

SP-B: is a member of the saposin gene family and the amoebapore gene superfamily. SP-B improves surfactant's surface activity by enhancing surface adsorption and surface stability of surfactant phospholipids. SP-B is encoded by a single-copy, 10-kilobase gene with 11 exons in chromosome 2p12-p11.2. The mature protein is coded by exons 6 and 7. (Whitsett 1995, Cole 2001) Also, in the absence of functional SP-B, alveolar SP-C is found in the precursor rather than functional form, with unknown clinical consequences. (Hallman 2002)

Rare SP-B mutations that result in lack of functional SP-B have been identified, including the 121ins2 frameshift mutation (Nogee 1993, 1994), and are associated with fatal respiratory disease at birth and abnormally formed and functioning alveolar type-2 cells. (Whitsett 1995) The exon 4 polymorphism, a missense mutation at nucleotide 1580 [C/T (1580)], which influences the amino acid sequence (Ile121Thr; the C at 1580 encodes Thr at codon 121) may have clinical consequences resulting from its affects on the consensus sequence for N-linked glycosylation in the N-terminal SP-B pro-peptide. (Lin 1998, Haataja 2000, Hallman 2002)

Studies of SP-A and SP-B Mutations and Risk of Respiratory Disease

Genetically-related severe surfactant protein B deficiency was the first reported cause of genetically caused respiratory distress syndrome in infants. Affected infants in a single kindred were homozygous for the exon 4 single base pair deletion and 3 base pair insertion of the surfactant protein B gene (121ins2). The only successful treatment for this disorder has been lung transplantation. (Nogee 1993, Cole 2001) In a large population-based cohort study, investigators found one 121ins2 allele per 3300 individuals by molecular ascertainment, and one per 1000 individuals from a Missouri cohort by clinical ascertainment. (Cole 2000)

In population studies, the most convincing evidence for more prevalent allelic polymorphisms with attributable risk for RDS has been seen in the SP-A alleles $6A^2$ and $1A^0$, and the SP-B Ile131Thr genotype. The most convincing results have come from Finnish, largely Caucasian, populations. (Hallman 2002) The largest study in the series reviewed by Hallman, conducted in 684 Finnish infants (184 premature infants with RDS and 500 premature controls), showed that risk of RDS was associated with the two SP-A alleles, and the associations were strongly associated with the SP-B Ile131Thr genotype together with the degree of prematurity ($\leq$ 32 weeks). The SP-B polymorphism was not independently associated with risk of RDS. (Haataja 2000)

In a multivariable logistic regression analysis which included gestational age (premature < or > 32 weeks), gender, and prenatal steroid treatment as independent co-variates, and presence or absence of SP-A1 polymorphisms $6A^2$ and $6A^3$, and SP-A2 polymorphism $1A^0$, SP-A alleles $6A^2$ and $1A^0$ were associated with increased risk and $6A^3$ with decreased RDS risk, and the associations were determined by SP-B Ile131Thr (nucleotide 1580 [C/T (1580)]genotype), with Thr/Thr homozygosity plus the degree of prematurity associated with RDS. For the study population, the allele frequencies were 0.60 for SP-A1 $6A^2$, that was associated with increased risk, and 0.28 for $6A^3$, associated with decreased risk. The allele frequencies for the SP-A2 alleles were 0.57 for the $1A^0$ allele associated with increased risk, and 0.16 for the $1A^1$ allele which showed a trend toward reduced risk. Unfortunately, the study did not define the clinical criteria for severity of RDS, or address subsequent pulmonary morbidity related to genotype or allele frequency. (Haataja 2000, Hallman 2002) Interestingly, the $6A^3$ allele was associated with reduced risk of RDS in another study, and was noted in higher frequency among African American infants vs. white infants. (Kala 1998)

In a candidate gene study of 19 SP-A, SP-B, and SP-D genes and SP-B flanking regions, using adult subjects from Germany, the SP-B, the C allele, at C/T (1580) was overrepresented in the group of German ICU patients with ARDS vs. controls (allele C 47.9% in controls vs. 62.5% in ARDS patients, odds ratio 0.412, 95% CI: (0.179, 0.878). In the group of patients with idiopathic ARDS 62.5% of

subjects were C/C (Thr/Thr) homozygotes, while only 12.8% of the control group were C/C (Thr/Thr) homozygotes. (Lin 2000)

After demonstrating correlations between SP-A genotypes with increased risk of RDS, Haataja et al performed transmission disequilibrium tests in a homogenous Finnish population (76 of mother-father-offspring < 32 weeks gestation with RDS trios and 31 "hypernormal" trios of mother-father-offspring < 32 weeks gestation without RDS trios) that the $6A^2$-$1A^0$ haplotype showed significant excess transmission to affected infants, wheras, the SP-A1 $6A^2$ allele was associated with decreased transmission in the non-RDS families. This study lacks definitions for severity of RDS, and included of only 35% of the potentially eligible trios. (Haataja 2001)

Surfactant protein polymorphisms to assess:
SP-A: $6A^2$; $6A^3$; $1A^0$.
There are multiple other mutations which may cause important changes in SP-A function which could be identified with microsatellite or complete SP-A1 and SP-A2 gene sequencing, but for this analysis, we propose focusing on these previously documented candidate alleles.

SP-B: SP-B C/T (1520), which causes the change from Thr to Ile within codon 131; SP-B 121ins2, the previously described lethal mutation which inserts an *Sfu1* restriction enzyme site.

As with SP-A, there are multiple less common "loss of function" SP-B alleles which could be examined with microsatellite or complete SP-B gene sequencing, but for this first analysis, we propose to examine only these previously documented candidate alleles.

Methods

Blood collection: Blood will be collected on filter paper cards on the first day of life when blood is ordered for routine tests by each subjects' physician. Blood spot cards on individual subjects labeled with their study numbers will be sent for storage and analysis to the Duke Center for Human Genetics.

DNA extraction: Genomic DNA will be extracted from the cards using standard techniques, (or amplified to genomic DNA by the multiple displacement amplification process, *see below*) for PCR cRFLP analysis. Methods will follow that described by Hamvas et al, with careful attention to removal of hemoglobin which can reduce efficiency of amplification. (Hamvas 2001)

Amplification As an alternative to DNA extraction from the blood spot cards, multiple displacement amplification will be used to produce up to 100 ug of DNA. The general assay technique is described by Hosono et al. who tested multiple displacement amplification (MDA) technique for whole genome amplification

(WGA) on buccal smears, whole blood, buffy coat samples and Guthrie cards. All tested loci for all methods were represented at > 50% of the starting genomic DNA on a copy per microgram DNA basis. Heme may be inhibitory to DNA polymerase, so use of very small sample volumes and, therefore, amounts of heme, avoids potential inhibition of Φ29 DNA polymerase. Hosono et al were able to amplify at least 10,000 fold increases in genomic DNA with 4 – 6 hour reaction times. They subsequently successfully used nanogram quantities of the amplified genomic DNA in TaqMan® assays (Applied Biosystems, Foster City, CA, USA) without prior DNA purification procedures. The authors also describe amplification of up to 7 mg of DNA in a 10 milliliter reaction. (Hosono 2003) Subsequently, investigators have produced microgram quantities of amplified DNA from 1 microliter blood samples and successfully assessed polymorphisms in hemoglobin genes. (Mai 2003)

Amplification SP-A1 and SP-A2 and SP-B SNP's will be done according to published methodologies using established primers and PCR using Taq polymerase.

Genotyping

Single nucleotide polymorphisms would be assessed using industry standard high-throughput genotyping. Currently, high throughput methodologies using real-time PCR such as TaqMan® technologies provided by Applied Biosystems, Inc (ABI, Foster City California) are industry and academic standards, and are much less labor intensive that PCR amplification followed by digests with restriction enzymes. ABI has more than 146,000 human SNP assays available. TaqMan® Assays-on-Demand™ SNP Genotyping Products comprise the largest collection of biologically informative, validated, pre-designed assays available anywhere. They are performed using the ABI PRISM® Sequence Detection System (SDSwhich is available at the Duke CHG.) The identity of SNPs is determined through the cluster analysis of the two-probe (VIC and FAM) end point analysis. Each point or cluster (multiple samples) will either show a FAM, VIC, or FAM/VIC fluorescence combination revealing the possible genotypes (2 homozyotes, 1 heterozygote). Results of the Taqman process are read electronically, and can be transferred to the sample database. From the sample database, the genotypes will be sent to RTI electronically.

If a requested SNP is not one of the 146,000 available at ABI, the company also produces "Assays by Design" which utilize the same high throughput technology. These ABI products, and the hardware required for PCR and reading are in place at the Duke CHG. For longer insertion and deletion genotyping, we will develop standard methods as described by Rämet et al. (Rämet 2000), or establish collaborations with investigators who have previously developed these genotyping assays.

Statistical Analysis Plan

Genotype counts and allele frequencies will be examined for the four polymorphisms in BPD/death infants and survivors without BPD, stratified by ventilation strategy treatment group. Allele frequency will be compared in the two groups with chi-square analysis, and will assess whether or not a specific allele is overrepresented in either outcome group. Additionally, multivariate analyses will be done for primary and selected secondary outcomes with inclusion of genotypes as variables in logistic regression models, to include interaction terms for SP-A $6A^2$ and $1A^0$ with SP-B Ile131Thr genotypes. Gestational age or birthweight, antenatal steroids, and treatment group will be included in the models. Analyses will be carried out for the entire population and stratified by race, as allele frequencies of the SP-A alleles could differ by race. (Kala 1998) As per the analysis by Haataja, et al, who showed a dependence of the SP-A genotype effects on presence of SP-B C/C1580 genotype, we will perform logistic regression analysis on the haplotype associations of the SP-A polymorphisms with the SP-B C/C 1580 (Thr/Thr) homozygote status.

Sample size

To evaluate the primary outcome in the Main COT study with 80% power, the planned sample size for the primary study is 1,170 infants, adding 15% attrition factor for a total of 1,345 infants.

For traditional genetic attributable risk case control studies for specific genotypes, with allele frequencies of 10% and 30% among controls and 20 to 90% among cases the following power/sample size table was previously generated

Power calculation for case-control study testing for significant differences in "at risk" genotype frequency between 100 death or BPD cases and 200 survivors without BPD (control) infants with various genotype frequency, and an alpha of 0.01.

Controls' "at risk" Genotype Frequency; n = 200	Cases' "at risk" Genotype Frequency; n = 100	Power
0.1	0.2	43%
	0.3	95%
0.2	0.4	85%
	0.6	> 95%
0.3	0.6	> 95%
	0.9	> 95%

The table was constructed with an alpha of 0.01 (anticipating multiple comparisons for several genotypes), to achieve power = 0.90.

There should be approximately 400 infants with the primary outcome variable of mortality/CLD, with a minimum 40% incidence. This will provide an adequate

sample size for multivariable analysis that includes consideration of at least three SP-A polymorphisms and one SP-B polymorphism (the rare SP-B 121ins2 mutation is not likely to be found with adequate frequency to be included in this analysis).

Summary

This study will provide an adequate sample size along with comprehensive clinical information to assessment of the interaction of genetic and other factors with risk of chronic lung disease among extremely premature infants. It will provide ample genomic DNA for future genetic association studies in this vulnerable population of infants.

Bibliography

Cole FS, Hamvas A, Rubinstein P, King E, Trusgnich M, Nogee LM, DeMello DE, Colten HR. Population-based estimates of surfactant protein B deficiency. Pediatrics 2000;105:538-541

Cole FS, Hamvas A, Nogee LM. Genetic disorders of neonatal respiratory function. Pediatric Research 2001;50:157-162)

Farrell PM, Wood RE: Epidemiology of hyaline membrane disease in the United States: analysis of national mortality statistics. Pediatrics 1976;58:167-176.

FlorosJ, Fan R. Surfactant protein A and B genetic variants and respiratory distress syndrome: allele interactions. Biology of the Neonate 2001;80:22-25

Haataja R. Ramet M, Marttila R, et al. Surfactant proteins A and B as interactive genetic determintants of neonatal respiratory distress syndrome. Hum Mol. Genetics 2000;9:2751-2760.

Haataja R, Marttila R, Uimari P, Lofgren J, Ramet M, Hallman M. Respiratory distress syndrome: evaluation of genetic susceptibility and protection by transmission disequilibrium test. Human Genetics 2001;109:351-355.

Hallman M, Arjomaa P, Mizumoto M, et al. Surfactant proteins in the diagnosis of fetal lung maturity. I. Predictive accuracy of the 35 kD protein, the lecithin/sphingomyelin ratio, and phostphatidylglycerol. Am J Obstet Gynecol. 1988; 158:531-535

Hallman M, Merritt TA, Akino T, et al. Surfactant protein A, phophatidylcholine, and surfactant inhibitors in epithelial lining fluid. Correlation with surface activity, severity of respiratory distress syndrome, and outcome in small premature infants. Am Rev. Respir Dis 1991;144:1376-1384.

Hallman M, Haataja R, Marttila R. Surfactant proteins and genetic predisposition to respiratory distress syndrome. Seminars in Perinatology 2002; 26:450-460.

Hamvas A, Trusgnich M, Brice H, Baumgartner J, Hong Y, Nogee LM, Cole FS. Population-based screening for rare mutations: high throughput DNA extraction and molecular amplification from Guthrie cards. Pediatric Research 2001; 50:666-668.

Hosono S, Faruqi AF, Dean FB, Du Y, Sun Z, Wu X, Du J, Kingsmore SF, Engholm M, Lasken RS. Unbiased whole-genome amplification directly from clinical samples. Genome Research 2003; 13:954-964

Kala P, Have TT, Nielsen H, Dunn M, Floros J. Association of pulmonary surfactant protein A (SP-A) gene and respiratory distress syndrome: Interaction with SP-B. Pediatric Research 1998;43:169-177.

Lakenau HM. A genetic and statistical study of the respiratory distress syndrome. European Journal of Pediatrics 1976;123:167-177.

Lin Z, deMello DE, Wallot M, Floros J, An SP-B gene mutation responsible for SP-B deficiency in fatal congential alveolar proteinosis. Evidence for a mutation hotspot in exon 4. Mol Genet Metab 1998;64:25-35.

Lin Z, Pearson C, Chinchilli V, Pietschmann SM, Luo J, Pison U, Floros J. Polymorphisms of human SP-A, SP-B, and SP-D genes: association of SP-B Thr131Ile with ARDS. *Clinical Genetics* 2000;58:181-191

Mai M, Hoyer JD, McClure RF Use of multiple displacement amplification to amplify genomic DNA before sequencing of the {alpha} and {beta} haemoglobin genes *J. Clin. Pathol* 2004;57:637 - 640

Nogee LM, de Mello DE, Dehner LP, Colten HR. Brief report: deficiency of pulmonary surfactant protein B in congential alveolar proteinosis. *N Engl J Med* 1993;328:406-410.

Nogee LM, Garnier G, Dietz HC, Singer L, Murphy AM, deMello DE, Colton HR. A mutatioin in the surfactant protein B gene responsible for fatal neonatal respiratory distress disease in multiple kindreds. *J Clin Investigation* 1994;93:1860-1863.

Pericak-Vance MA, Grubber JM, Bailey LR, Hedges D, West S, Santoro L, Kemmerer B, Hall JL, Saunders AM, Roses AD, Small GW, Scott WK, Conneally PM, VANCE JM, Haines JL. Identification of novel genes in late-onset Alzheimer disease. *Experimental Gerontology*, 2000; 35:1343-1352,

Rämet M, Haataja R, Marttila R, Floros J, Hallman M Association between the surfactant protein A (SP-A) gene locus and respiratory-distress syndrome in the Finnish population. *Am. J. Hum. Genet.,* 66:1569-1579, 2000

. Scott WKNance MA, Watts RL, Hubble JP, Koller WC, Lyons K, Pahwa R, Stern MB, Amy Colcher A, Hiner BC, Jankovic J, Ondo WG, Allen FH, Goetz CG, Small GW, Masterman D, Mastaglia F, Laing NG, Stajich JM, Slotterbeck B, MW, Ribble RC, Rampersaud E, West SG, Gibson RA, Middleton LT, Roses AD, Haines JL, Scott BL, Vance JM, Pericak-Vance MA. Complete Genomic Screen in Parkinson Disease: Evidence for Multiple Genes. *JAMA* 2001; 286(18) 2239-2244.

Whitsett JA, Nogee LM, Weaver TE, Horowitz AD. Human surfactant protein B: structure, function, regulation and genetic disease. Physiologic Review 1995;75:749-757.

From: Petrie, Carolyn

To: Petrie, Carolyn; 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)"; "Brenda Poindexter (bpoindex@iupui.edu)"; "CARL D"ANGIO (Carl_Dangio@urmc.rochester.edu)"; "Danny Benjamin (BENJA005@onyx.dcri.duke.edu)"; "Krisa Van Meurs (vanmeurs@leland.stanford.edu)"; "M. D Kurt Schibler (kurt.schibler@cchmc.org)"; " (RSchelonka@peds.uab.edu)"; "Martin Blakely (martin.l.blakely@uth.tmc.edu)"; "Mike Cotten (cotte010@mc.duke.edu)"; "Brenda Morris MD (Brenda.H.Morris@uth.tmc.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)"; "Monica Collins (mcollins@peds.uab.edu)"; "Lucy Miller (lucmille@iupui.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)"; Hastings, Betty J.; Das, Abhik; " (bsood@med.wayne.edu)"; "M. D. Susan Hintz (srhintz@stanford.edu)"; "Maynard Rasmussen (maynard.rasmussen@sharp.com)"; "Susie Buchter (susie.buchter@oz.ped.emory.edu)"; Shirley Cosby (scosby@peds.uab.edu)

Cc: "Alice Reardon (Houston) (Alice.J.Reardon@uth.tmc.edu)"; " (bvecchio@careNE.org)"; "Debbi MacDougall (dmacdoug@iupui.edu)"; "Debbie Camputaro (debra.camputaro@yale.edu)"; "Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)"; "Heidi Squibb (UCSD) (hsquibb@ucsd.edu)"; " (Karen.Kirby@UTSouthwestern.edu)"; " (Ktownsen@med.wayne.edu)"; " (Kristina_Mossgraber@urmc.rochester.edu)"; "Lisa Joo (Stanford) (lisa.joo@stanford.edu)"; "Marsha Sumner (UAB) (msumner@peds.uab.edu)"; " (mlg@cwru.edu)"; [SCRN] Dunbar-Scott, Renee; "Sharon Gonzales (Duke) (gonza025@mc.duke.edu)"; "Wendy Holcomb"; Roberts, Sarah (NIH/NICHD); Scholl, Diane (NIH/NICHD)

Subject: SUPPORT conference call, Mon. Jun. 21, 12-2pm EDT

Date: Thursday, June 17, 2004 2:47:36 PM

For those who are unable to attend the SUPPORT meeting at the Neonatal Research Network Steering Committee meeting on **Monday, June 21, 12:00-2:00pm EDT (9:00-11:00am PDT)**, we have arranged a conference line for you or the center PI to join via telephone.

To join the call:

Dial Tollfree: **866-675-**(b) (6)

Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

Thank you,
Carolyn Petrie

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

From: Neil Finer
To: Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"; "Michele"
Subject: RE: SUPPORT Call
Date: Thursday, June 10, 2004 6:03:33 PM

Thanks Ed
I will fix. I have read this thing so many times that I am not seeing all the details. On the issue of must and may, we had discussed this and I believe that we concluded in response to a number of critiques that we wanted the clinicians to follow the protocol. If they choose not to extubate we will have that data. I personally could live with MAY, but I do recall this discussion.
I have copied this part of the protocol below. I will ask everyone to look at this section – The Extubation Criteria for Control Infants.

"**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 ≥ 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 (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.

Be well
Neil

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Thursday, June 10, 2004 2:31 PM
To: nfiner@ucsd.edu
Subject: Re: SUPPORT Call

Neil,

A couple of minor details in the protocol that you sent yesterday.

The duration of the intervention is listed as 14 days for both strata in the CPAP arm, 7 days for the 26-27 stratum of the control arm and 14 days for the 24-25 wk stratum. Shouldn't these all be the same?

Also, for the control arm, the indications for extubation are "musts". I thought that this was supposed to be "may" so that if clinicians wanted to keep them intubated a little longer, it really wouldn't hurt the study.

Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 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

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: SUPPORT Training Participants List
Date: Thursday, June 03, 2004 3:30:16 PM

Hey Rose, see below.

I am not sure what is involved with (b) (6) but what if we ask Abbot just to come on the 14th.

Carolyn

-----Original Message-----
From: Angelita Hensman [mailto:AHENSMAN@CareNE.org]
Sent: Thursday, June 03, 2004 3:08 PM
To: petrie@rti.org
Subject: Re: SUPPORT Training Participants List

Hi Carolyn: There is no way Dr. Laptook can do these dates. It is the (b) (6) (b) (6) and this is why we had previously let you know that only the 8th and 9th were good. I realize that the majority of centers were probably available for the 14th -16th. Not sure how to resolve this. Let me know.
Thanks
Angelita

>>> Petrie, Carolyn 06/03/04 01:53PM >>>
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

From: Neil Finer
To: "Edward Donovan"
Cc: Shahnaz Duara; Avroy A. Fanaroff, M.D.; Ed Donovan; Higgins, Rosemary (NIH/NICHD); Neil Finer; "Wade Rich"; "Michele"
Subject: RE: SUPPORT training
Date: Monday, May 17, 2004 7:48:12 PM

Hi Ed
I have a number of thoughts.
Does anybody actually give CPAP alone by ETT?
Should we ask only about the ELBW infant as this is what SUPPORT will study?
I would also like to ask the following – What are/is the commonest problem(s) that you encounter while trying to deliver CPAP – nasal erosion, prongs falling out, infection, bleeding, adequate seal, patency, especially for long prongs.
How do you assure that you are delivering the preset pressure?
Do you determine/ensure that the mouth is closed when giving CPAP?
I thought Wally's comments were very useful
I hope that these comments are helpful.
Neil

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Monday, May 17, 2004 1:41 PM
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:	Petrie, Carolyn
To:	Charles Rosenfeld (crosen@mednet.swmed.edu); M. D. Abbot Laptook (alaptook@WIHRI.org); M. D. Avroy A. Fanaroff (aaf2@cwru.edu); [SCRN] Stoll, Barbara; M. D. Dale L. Phelps (dale_phelps@urmc.rochester.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); Renee Bridge (rbridge@ucsd.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); Krisa Van Meurs (vanmeurs@leland.stanford.edu); Mike Cotten (cotte010@mc.duke.edu); Vivek Narendran (Vivek.Narendran@cchmc.org)
Cc:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; Hastings, Betty J.; Petrie, Carolyn; Das, Abhik
Subject:	SUPPORT Trial Contact List
Date:	Friday, May 14, 2004 4:32:48 PM
Attachments:	SUPPORT Trial Contact List.doc

Attached is a draft contact list for the SUPPORT trial (in order by center number). Please review your center's information and send me any updates by Wednesday, May 19.

We would like the SUPPORT study PIs to attend this June 21-22 NRN Steering Committee meeting as we will schedule a two hour meeting to discuss the SUPPORT trial.

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

SUPPORT Trial Contact List

Case Western
Center 3

Study PI Dr. Michele Walsh Email: mcw3@cwru.edu Phone: (216) 844-3387	**Respiratory Therapist** Mike Tracey RT Email: Phone:
Study Coordinator Nancy Newman RN Email: nxs5@cwru.edu Phone:216-368-3084	**Research Nurses** Bonnie Siner RN Email: Phone:

SUPPORT Trial Contact List

UT-Dallas
Center 4

Study PI Dr. Walid Salhab Email: Walid.Salhab@utsouthwestern.edu Phone: 214 648 3753	**Respiratory Therapist** James Allen Email: JRALLE@parknet.pmh.org Phone: 214 590 8193 and 972.396.1920
Study Coordinator Gaynelle Hensley Email:gaynelle.hensley@utsouthwestern.edu Phone:214-648-3780	**Research Nurses** Della Feeha Email: DFEEHA@parknet.pmh.org Phone:214 590 6500

SUPPORT Trial Contact List

Wayne State
Center 5

Study PI Dr. Seetha Shankaran Email: sshankar@med.wayne.edu Phone: 313-745-1436	**Respiratory Therapist** Rontriece Turner
Study Coordinator Rebecca Bara Email: ae5357@wayne.edu Phone:313-745-1436	**Research Nurses**

SUPPORT Trial Contact List

Miami
Center 8

Study PI Dr. Shahnaz Duara Email: sduara@miami.edu Phone: (305) 585-6408	**Respiratory Therapist** Lucille Fasone Email: Phone:
Study Coordinator Ruth Everett Email: reverett@med.miami.edu Phone:305-585-8433	**Research Nurses** Janet Mitchell Email: Phone:

SUPPORT Trial Contact List

Emory
Center 9

Study PI Dr. Susie Buchter Email: susie.buchter@oz.ped.emory.edu Phone: (404) 778-1413	**Respiratory Therapist** Email: Phone:
Study Coordinator Ellen Hale Email: ellen_hale@oz.ped.emory.edu Phone:404-616-4218	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Cincinnati
Center 11

Study PI Dr. Vivek Narendran Email: Vivek.Narendran@cchmc.org Phone: (513) 558-0557 Kurt Schibler Email: kurt.schibler@cchmc.org Phone: (513) 636-3972	**Respiratory Therapist** Sandy McClanahan Email: Phone: Dave Mane Email: Phone: Eric Stephenson Email: Phone:
Study Coordinator Cathy Grisby Email: grisbyca@email.uc.edu Phone: (513) 558-4953	**Research Nurses** Pam Krieg Deb Riedinger, Bonnie Eilerman, Pasty Uebel

SUPPORT Trial Contact List

Indiana
Center 12

Study PI Dr. James Lemons Email: jlemons@iupui.edu Phone: (317) 274-4716	**Respiratory Therapist** Email: Phone:
Study Coordinator Lucy Miller Email: lucmille@iupui.edu Phone:317-278-7809	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Yale
Center 13

Study PI Dr. Vineet Bhandari Email: vineet.bhandari@yale.edu Phone: 203-688-2320	**Respiratory Therapist** Email: Phone:
Study Coordinator Pat Gettner Email: pat.gettner@yale.edu Phone: 203-688-7987	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Brown
Center 14

Study PI Dr. William Oh Email: WOh@wihri.org Phone: (401) 274-1122 ext 1432	**Respiratory Therapist**
Study Coordinator Angelita Hensman Email: ahensman@wihri.org Phone: (401) 274-1122 x1730	**Research Nurses**

SUPPORT Trial Contact List

Stanford
Center 15

Study PI Dr. Krisa Van Meurs Email: vanmeurs@leland.stanford.edu Phone: 650 723-5711	**Respiratory Therapist** Email: Phone:
Study Coordinator Bethany Ball Email: mbball@leland.stanford.edu Phone: (650) 725-8342	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Alabama
Center 16

Study PI Dr. Wally Carlo Email: wcarlo@peds.uab.edu Phone: (205) 934-4680	**Respiratory Therapist** Robert Johnson Email: Phone:
Study Coordinator Monica Collins Email: mcollins@peds.uab.edu Phone:205-934-5771	**Research Nurses**

SUPPORT Trial Contact List

UT-Houston
Center 18

Study PI Dr. Brenda Morris Email: Brenda.H.Morris@uth.tmc.edu Phone:	**Respiratory Therapist** Email: Phone:
Study Coordinator Georgia McDavid Email: Georgia.E.McDavid@uth.tmc.edu Phone: 713-500-5734	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

Duke
Center 19

Study PI Dr. C. Michael Cotten, MD Email: cotte010@mc.duke.edu Phone: (919) 681-0630	**Respiratory Therapist** Denise Lawson, RRT Email: lawso003@mc.duke.edu Phone: (919) 668-3328
Study Coordinator Kathy Auten Email: auten002@mc.duke.edu Phone: 919-681-5859	**Research Nurses** Kathy Foy, RN Email: foy00004@mc.duke.edu Phone: (919) 668-3360 Josette Collen, RN Kelle Shiflett, RN Valerie Jensen, RN

SUPPORT Trial Contact List

Rochester
Center 21

Study PI Dr. Nirupama Laroia Email: Phone:	**Respiratory Therapist** Email: Phone:
Study Coordinator Linda Reubens Email: linda_reubens@urmc.rochester.edu Phone: (585) 275-0218	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

UC-San Diego
Center 22

Study PI Dr. Neil Finer Email: nfiner@ucsd.edu Phone: (619) 543-3759	**Respiratory Therapist** Jim Goodmar Email: Phone:
Study Coordinator Wade Rich Email: wrich@ucsd.edu Phone: 619-543-5375	**Research Nurses** Renee Bridge Email: rbridge@ucsd.edu Phone:

SUPPORT Trial Contact List

Wake Forest
Center 20

Study PI Dr. T. Michael O'Shea Email: moshea@wfubmc.edu Phone: (336) 716-2529	**Respiratory Therapist** Email: Phone:
Study Coordinator Nancy Peters Email: npeters@wfubmc.edu Phone: (336) 716-6911	**Research Nurses** Email: Phone:

SUPPORT Trial Contact List

RTI International
Data Coordinating Center

Study PI Dr. Ken Poole Email: poo@rti.org Phone: 919-485-7721	**Alternate Study PI** Dr. Abhik Das Email: das@rti.org Phone: 301-230-8214
NICHD Liaison Coordinator Carolyn Petrie Email: petrie@rti.org Phone: 301-230-4648	**Protocol Coordinator** Betty Hastings Email:bkh@rti.org Phone: 919-485-7740

SUPPORT Trial Contact List

NICHD

Program Scientist Dr. Rosemary Higgins Email: higginsr@mail.nih.gov Phone: 301-435-7909	

From: Neil Finer
To: "Duara, Shahnaz"; "Avroy A. Fanaroff, M.D."; "Ed Donovan"; Higgins, Rosemary (NIH/NICHD); "Wade Rich"
Cc: "Michele Walsh-Sukys"; wrich@ucsd.edu
Subject: RE: SUPPORT
Date: Wednesday, May 12, 2004 7:23:46 PM

This looks OK to me. Are the rest of you OK with this approach?
Neil

-----Original Message-----
From: Duara, Shahnaz [mailto:SDuara@med.miami.edu]
Sent: Wednesday, May 12, 2004 6:39 AM
To: Neil Finer; Avroy A. Fanaroff, M.D.; Ed Donovan; higginsr@mail.nih.gov; Wade Rich
Cc: Michele Walsh-Sukys
Subject: RE: SUPPORT

Hi Neil,

No, there is no formula - it is more that the numbers are looked over by experienced nurses - if there were 2 values recorded with equal frequency (rare event, I am told) the average of the two would be taken as the value for the day.
Hope this helps.
Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, May 11, 2004 5:17 PM
To: Duara, Shahnaz; Avroy A. Fanaroff, M.D.; Ed Donovan; higginsr@mail.nih.gov; Wade Rich
Cc: Michele Walsh-Sukys
Subject: Re: SUPPORT

Hi Shahnaz
How do you get the day's median? Is there a formula or is it more by looking over the numbers by experienced nurses/RCPs? If there are 2 values with equal frequency which is chosen or do you then do an average. Please let us know and we could add to the manual. This would facilitate the data collection which we are trying to keep as simple as possible
Many thanks for this information
Neil

----- Original Message -----
From: Duara, Shahnaz
To: nfiner@ucsd.edu ; Avroy A. Fanaroff, M.D. ; Ed Donovan ; higginsr@mail.nih.gov ; Wade Rich
Cc: Michele Walsh-Sukys
Sent: Tuesday, May 11, 2004 9:07 AM
Subject: RE: SUPPORT

Dear Neil,

Recording just pH and PaCO2 makes sense to me. With respect to the FiO2, I'm not sure three times a day will be representative of what is going on, particularly for babies with fluctuating O2 needs. We track FiO2 in Miami for all babies < 1000g and <31 weeks GA daily for as long as they are in O2. We treat the day as a 24 hr block and determine the most frequent FiO2 (like a median value) to be the day's FiO2. Tracking 250-300 babies annually takes an experienced nurse 2 days twice a

month. Should we consider something similar for the protocol?

Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, May 07, 2004 4:12 PM
To: Duara, Shahnaz; Avroy A. Fanaroff, M.D.; Ed Donovan; higginsr@mail.nih.gov; Neil Finer; 'Wade Rich'
Cc: Michele Walsh-Sukys
Subject: SUPPORT

Hi Everyone
I reviewed the SAVE data forms and the Benchmarking forms. We can't find any data entry for FiO2 for SAVE apart from the eligibility form. Benchmarking has a form for days 1, 3, 7. We will modify this one. If you know of any other such forms please let me know. We are going to keep the data to a minimum. I suggest that we only want pH and PaCO2 from the gases, and a measure of FiO2 3 times /day till day 14 then once/day while on Oxygen.
I would appreciate your thoughts.
Thanks
Neil

From: Hastings, Betty J.
To: Higgins, Rosemary (NIH/NICHD)
Subject: SUPPORT
Date: Friday, May 07, 2004 2:28:15 PM

I just talked to Neil and Wade and we have a plan. Hopefully we will have a draft of the forms (and maybe the manual) for the June meeting. The will be looking at the SAVE forms and give me more of a concrete idea of what they want to collect.

Also, I still haven't receive the HUS from Georgia. I just may have to get someone to send them to Carolyn next week, along with the forms and labels. Sorry about that.

Betty

Betty Hastings

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

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Cc: Neil Finer
Subject: O2 sat pilot
Date: Thursday, April 29, 2004 7:20:49 AM

Rose: Neil suggested that we make the first secondary objective (separation of O2 sats) the primary one. I think that would be ok but should discuss pros and cons, as this has already been shown in the BOOST trial. I was trying to come up with an innovative primary outcome as when FiO2 is decreased, PaO2 may not drop so much because of physiological or pathological shunts that can affect the oxygenation index. Wally

---

From:	Wally Carlo, M.D.
To:	Edward Donovan; aaf2@cwru.edu; mcw3@cwru.edu; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; petrie@rti.org; poo@rti.org; nfiner@ucsd.edu
Cc:	Diane Timmer; mlg@cwru.edu; Mvalles2@med.miami.edu; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
Subject:	RE: SUPPORT conf call, Fri May 7, 11am-12pm EDT (10-11am CDT)
Date:	Tuesday, April 27, 2004 11:48:38 PM

Hi; I will be sending the protocol ton O2 sats tomorrow. Wally

---

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Thursday, April 22, 2004 9:41 AM
To: aaf2@cwru.edu; mcw3@cwru.edu; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; petrie@rti.org; poo@rti.org; nfiner@ucsd.edu
Cc: Diane Timmer; mlg@cwru.edu; Mvalles2@med.miami.edu; adas@rti.org; bkh@rti.org; hsquibb@ucsd.edu
Subject: Re: SUPPORT conf call, Fri May 7, 11am-12pm EDT (10-11am CDT)

What about the other secondaries?. I understand from Neil that several have been submitted.

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

>>> "Petrie, Carolyn" <petrie@rti.org> 04/22/2004 10:09:05 AM >>>

The SUPPORT conference call to discuss the protocol and Dr. Hintz's secondary (attached) is scheduled for:

Friday, May 7

11am-12pm EDT (10-11am CDT)

To join the call:

Dial Tollfree: (b) (6)

Passcode: (b) (6) (# when prompted)

Leader: Rose Higgins

If you are unable to join the call, please submit your comments to the group by Thursday, May 6.

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: Neil Finer
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Re: SUPPORT Protocol
Date: Tuesday, March 16, 2004 9:55:50 PM

G'day mate
I see you already have the lingo
Hemodynamic stability is going to be in the eyes of the beholder
It will vary from site to site but you could select "Infants for whom blood pressure support in the form of volume pushes or inotropic agents were not administered"
We will have problems if we start selecting blood pressures, heart rate, cap refill,cardiac output by ECHO, IVC flow by ECHO , etc
have a great time down under
Av

At 06:17 PM 3/16/2004 -0800, you wrote:

> 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: Avroy A. Fanaroff
To: nfiner@ucsd.edu; Edward.Donovan@chmcc.org; sduara@miami.edu; Higgins, Rosemary (NIH/NICHD); WCarlo@PEDS.UAB.EDU
Subject: RE: COT ?Final Protocol
Date: Friday, March 12, 2004 9:43:11 AM

Reluctantly I must agree with Wally
Also if there is a self extubation and the baby flies is that a violation?
Av

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

From: Wally Carlo, M.D.
Date: 03/12/04 08:29:12
To: 'nfiner@ucsd.edu'; Ed Donovan; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.
Subject: RE: COT ?Final Protocol

Neil et al.: The protocol violations should be when the MUST actions are not performed. In the section of extubation you make the protocol too strict by requiring all 4 criteria for a MUST extubate but then if anyone is absent, extubation would be a violation. This gives no room for clinical judgment. MUST actions should be done to assure something is done but clinicians need some flexibility to be able to make decision, such as extubation in this case, (and we also want that to happen) when not all four extubation criteria are met. Wally
-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, March 11, 2004 8:30 PM
To: Ed Donovan; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; 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 O_2, 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: Michele Walsh
To: Goldberg, Ron; Hererra, Carmen M
Cc: Higgins, Rosemary (NIH/NICHD); Yao, Qing
Subject: Fw: Extubation protocol: Sample size and data collection tool
Date: Tuesday, March 09, 2004 4:15:26 PM

Carmen:
Bench will conclude in May 31 2004. (Originally we had thought it might continue until September in some centers, but that is not correct.)
We can expect to recruit 42/month for a total of 84 patients in the time remaining. If I read it correctly your smallest sample size is a minimum of 170 infants to detect a 20% change in death
with 80% power. I would encourage you to go for the more important and more likely endpoints of BPD or trach related to failed extubation which will require a far larger sample size as you have shown. This could be done as a secondary to the COTrial- but not within the time remaining in benchmarking. Please let me know if I have misunderstood something, or if you want to revert to a retrospective design using our existing data recognizing the substantial limitations of that data set.
Regards, Michele

----- Original Message -----
From: Yao, Qing
To: 'Michele Walsh' ; Yao, Qing ; Poole, W. Kenneth
Cc: Goldberg, Ron
Sent: Monday, March 08, 2004 12:40 PM
Subject: RE: Extubation protocol: Sample size and data collection tool

Hi, Michele,

I checked the sample sizes in Table 5 and 6. They are right for comparing two proportions specified with alpha=0.05 and equal sample size on two arms. But extubation failure and sucess groups may not have equal numbers, as a result, the sample size may need to be slightly higher than those in the table depending on how imbalance the two groups will be. (For example, if one group may have twice the number of the other group, the number in the first cell in Table 5 will be 193 rather than 170).

Let me know if you have any questions,

Thanks,

-Qing

> -----Original Message-----
> **From:** Michele Walsh [mailto:mcw3@po.cwru.edu]
> **Sent:** Friday, March 05, 2004 3:17 PM
> **To:** Yao, Qing; Poole, Ken
> **Cc:** Goldberg, Ron
> **Subject:** Fw: Extubation protocol: Sample size and data collection tool
>
> Hi: This is from an investigator at Duke who has proposed a secondary to the Benchmarking. The problem is that the data does not exist within Bench currently, so additional data would need to be collected. Given the approaching close of the study, we asked her to project a sample size to see if it was even possible to

collect the data that she is interested in.
Could you review pls? Do you agree with the sample size projections? (They seem too low to me.)
Thanks.
Michele
----- Original Message -----
From: Carmen M Hererra
To: Michele Walsh
Cc: Ronald N Goldberg ; Michael Cotten
Sent: Thursday, February 26, 2004 8:44 PM
Subject: Extubation protocol: Sample size and data collection tool

Hi Michele,

Initially I thought the analysis had to be done by epochs of 7 days because this is the way mechanical ventilation data are collected in the GDB respiratory support form (NG07). I thought we could query the database for the number of cumulative days on mechanical ventilation in each epoch: at 24 hours, day 7, day 14, day 21, and day 28, allowing for the identification of infants who were reintubated within any one epoch. The problem with this approach is that we are likely to miss babies who get reintubated within 24 hours. Collecting the date and time of extubation and reintubation prospectively will be certainly much more accurate.

Attached are the sample size considerations and a data collection tool. According to my calculations, if we start collecting the data soon, there should be enough patients to detect a difference of 15% in mortality with a 90% power (N=386) and a 15% increase in death/BPD with an 85% power (N=392), alpha error of 0.05 and 2-sided test. Concerning the data collection tool, it would be ideal to have all this information. However, if this is not practical, the critical data to collect are only date & time of extubation occurring within the first 28 days of life and date & time of reintubation if reintubation occurs within 7 days of extubation. Also, I don't think the analysis across groups should be a major issue because this is mostly an hypothesis generating study,

Regards,

Carmen

"Michele Walsh" <mcw3@po.cwru.edu>

02/20/2004 03:32 PM

To: "Carmen M Hererra" <herre004@mc.duke.edu>
cc:
Subject: Re: Protocol

Carmen:
We reviewed your protocol and felt that it may make an interesting

secondary to the Bench study.
Unfortunately, we did not collect data
on extubations or failures. We wondered
if you had a plan to create this data from our existing
forms. We also suggested a sample size analysis
to determine if there will be sufficient pts enrolled in
the remaining 6 months of the study to be able to
do a small ancillary data collection tool that would
collect this data prospectively. We would ask that
this data be analyzed across groups (that is not broken
out by randomized or control centers) so as not to
compromise the main trial. I regret that my delays
may have impaired your ability to get this study done;
I did not understand that additional data might need to
be collected. Regards, Michele

----- Original Message -----
From: Carmen M Hererra
To: mcw3@po.cwru.edu
Cc: Ronald N Goldberg ; Michael Cotten
Sent: Tuesday, February 17, 2004 5:41 PM
Subject: Re: Protocol

Hi Michele,

Ron and Mike told me this protocol was discussed at the most recent Benchmarking subcommittee meeting and that I needed an addendum including the specific dates of extubation (and reintubation for those babies who failed) to the data collection form. My understanding is that this information could be obtained from approximately 400 babies that are to be recruited yet. Would you please tell me the specifics of the procedure to follow?

I really appreciate your help,

Carmen

Michele Walsh <mcw3@po.cwru.edu>

01/09/2004 03:07 PM

To: Carmen M Hererra <herre004@mc.duke.edu>
cc:
Subject: Re: Protocol

Carmen:
I will distribute for discussion at the Benchmarking subcommittee meeting
in January.
Michele
----- Original Message -----

From: Carmen M Hererra <herre004@mc.duke.edu>
To: Michele Walsh-Sukys <mcw3@cwru.edu>
Cc: Michael Cotten <cotte010@mc.duke.edu>; Ronald N Goldberg <goldb008@mc.duke.edu>
Sent: Thursday, December 18, 2003 3:04 PM
Subject: Protocol

>
>
>
>
> Hi Michele,
>
>
> Attached is the proposal for querying the "Benchmarking to reduce
BPD"
> study and the GDB databases. The purpose is to assess the risks of
> morbidity (BPD in particular) and mortality associated with extubation
> failure in babies with BW<1251 grams.
>
> The use of propensity scores for the analysis is particularly
useful
> in this case because it allows the stratification of infants by their
> conditional probability of extubation failure given observed prognostic
> variables; therefore, the comparison extubation failure versus success is
> expected to be balanced with respect to these prognostic variables (ie.
the
> prognostic variables for extubation failure will not be predictive of the
> outcome death/BPD).
>
> I know the holidays are fast approaching, but I would greatly
> appreciate it if you could take a look at it when you have a chance.
>
> Happy holidays,
>
> Carmen
>
>
>
>
> (See attached file: Extubation Failure September 03.doc)
>

From: Neil Finer
To: Poole, W. Kenneth
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: COT Trial
Date: Friday, March 05, 2004 4:23:54 PM

Thanks
Ken
Can you provide me with the required sample size for using a by center by week randomization. In addition I will have Wade write to you regarding the plans for analyzing the SpO2 data from the POs. We will try to make this simple, they will be Excel files, and possibly be one file per week - 2 weeks per baby depending on the sampling frequency,
Thanks
Neil

> ----- Original Message -----
> **From:** Poole, W. Kenneth
> **To:** 'Neil Finer'
> **Sent:** Friday, February 27, 2004 10:55 AM
> **Subject:** RE: COT Trial
>
> I would prefer a simple random sampling approach but it appears this is less than desirable for the coordinators and others involved. I didn't wade through Jon's 14 page review so I don't know what "methodological" problem he has with the randomization by week. If this is the way we're going, we need to have another look at the sample size. As I mentioned to you, the numbers in the protocol (1/20/2004 version) assume simple random sampling and the adjustment of 12% I mentioned assumed we were randomizing by multiples. If we randomize by week, then the cluster size could be significantly larger than for multiples and hence would increase the sample size.
>
> > -----Original Message-----
> > **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> > **Sent:** Thursday, February 26, 2004 4:30 PM
> > **To:** Poole, W. Kenneth
> > **Subject:** Re: COT Trial
> >
> > Thanks Ken
> > What is your wish? I would like to go forward with by week randomization by site to support the coordinators who feel that this study would be much easier to perform with this process. I also know that some - read J Tyson - would be opposed on methodological grounds.
> > Also please send me any suggested names as we have been requested to try for something other than COT.
> > I like RAPOP Study-Comparison of Respiratory and Pulse Oximetry in Prematures- Sounds like Hip-hop!! or CRAPOP for ContinuousRAPOP
> > I know this is bad but it should get your juices flowing.
> > Be well
> > Neil
> >
> > > ----- Original Message -----
> > > **From:** Poole, W. Kenneth
> > > **To:** 'Neil Finer'
> > > **Sent:** Tuesday, February 24, 2004 12:14 PM
> > > **Subject:** RE: COT Trial
> > >
> > > We will try to do as the coordinators wish. I'm not sure for the reason of the imbalance in the pilot but my impression is that it was because of a couple of "good weeks"at some of the centers. Messing with the randomization system at mid stream will be cumbersome but

we will deal with it.

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, February 17, 2004 12:08 PM
To: Poole, W. Kenneth
Cc: wrich@ucsd.edu; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: COT Trial

Ken
It looks like the COT trial will move ahead.
The site coordinators are united in the belief that randomization by site by week would enormously facilitate this trial. Now that we are randomizing families as a unit and have made a power adjustment, can you determine if the imbalance in the Pilot was from multiples or some other factor? In addition, if we did site by week or something similar, could we after 1/3 and 2/3 enrollment alter the weeks to regain balance?
I know that we have discussed this before, but I would like one more attempt to respond to the coordinators who after all, are the workhorses and know their environments very well indeed.
Many thanks for giving this idea some consideration
Regards
Neil Finer

From: Neil Finer
To: Abbot Laptook, MD
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: COT
Date: Monday, March 01, 2004 5:20:08 PM

I think that your interpretation is correct. Thus at theses limits, the PO will alarm when it is outside the limits, ie at 84% and 96% which will be reality. The chart was showing the actual SpO2 at the limit setting, not how the alarms would function - that is the actual SpO2 at which the alarm would sound etc.
I have rewritten the table to clarify and added the following sentence as well.

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

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.
Thanks Abbot
Neil

----- Original Message -----
From: Abbot Laptook, MD
To: nfiner@ucsd.edu
Cc: Walid.Salhab@utsouthwestern.edu ; [mail.nih.gov].HigginsR
Sent: Thursday, February 26, 2004 6:07 AM
Subject: Re: COT

Neil,
Thanks for the clarifications. I am in Rhode Island but I go back to Dallas every other month until June to make sure that the site is functioning well. I hate to bug you but I have one more question regarding the protocol. With regards to the pulse oximeter arm, I don't understand why there is a difference between the CRT output alarms and the actual alarms as indicated on the table, page 18 of the protocol. When I look at the figure comparing actual vs low and hi reading SaO2, I can't see why the actual alarms shouldn't be 85 and 95 for both groups. I assume that when the alarm is set at 85%, it alarms when it hits 84%, and at the high end when the alarm is set at 95%, it alarms at 96% (similar to the Nellcor). All the points converge to one at 84 and 96%, so why is there the difference stated in the table? Let me know, Thanks, Abbot

>>> Neil Finer 02/25/04 01:49PM >>>
Thanks Abbot
I appreciate your meticulous review.
The protocol is correct for
1. We have removed pH as a criteria for intubation of the Treatment group
2. The protocol should also read equal to or less than 15, and >.
50. I think my underline didn't work here
3. The Protocol is correct - Reintubation should be performed if the FiO2 is greater than .4 for Control infants.
4. Abbot you are correct, the title is incorrect. I will correct both the

protocol and the PowerPoint. Rose wants a final version by Mid March and I will include all of these.
So, are you in Rhode Island or Dallas??
Wherever, Be well
Neil

----- Original Message -----
From: "Abbot Laptook, MD" <ALaptook@wihri.org>
To: <nfiner@ucsd.edu>
Cc: "Rosemary Higgins" <HigginsR@mail.nih.gov>;
<Walid.Salhab@utsouthwestern.edu>
Sent: Tuesday, February 24, 2004 2:37 PM
Subject: COT

Neil
In the process of reviewing the study for presentation to the faculty and fellows here at Brown and at UT, Walid and I came across a few differences between your slides and the protocol. I certainly hope I have the latest version of your slides (I think so).
1) slide 2: intubation criteria lists a ph<7.2 and the protocol does not have this
2) slide 3: extubation criteria lists a rate of less than or equal to 15 but the protocol states just <. FiO2 is listed as <.5 and the protocol lists as less than or equal to.
3) slide 5: reintubation criteria in the slide state FiO2 greater than or equal to .4 but the protocol is just >.
4) slide 10: CLD should be ROP.
Let me know, Abbot

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: CPAP
Date: Monday, March 01, 2004 3:55:59 PM

That is our best guesstimate. I would suggest that we ask for 225 on the low end. If we want to keep infants on till they are off of all oxygen, then we will have less units to recycle per NICU, and could lose enrollments. We will attempt to recalculate and get back to you within 24 hours
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Sent: Friday, February 27, 2004 11:00 AM
Subject: CPAP

Neil
Things are looking very positive for co-funding for the DR CPAP study. Let me know how many oximeters we will need (I think we had estimated 200).
Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From:	Neil Finer
To:	Abbot Laptook, MD
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: COT
Date:	Monday, March 01, 2004 3:49:15 PM

Abbot
What if we changed the wording to indicate that it is recommended that surfactant be given within the first 48 hrs for infants with evidence of respiratory distress?
Neil
----- Original Message -----
From: "Abbot Laptook, MD" <ALaptook@wihri.org>
To: <nfiner@ucsd.edu>
Cc: "Rosemary Higgins" <HigginsR@mail.nih.gov>;
<Walid.Salhab@utsouthwestern.edu>
Sent: Friday, February 27, 2004 12:13 PM
Subject: COT

Neil
Another COT issue. Walid has presented the COT proposal to the Dallas group and one particular issue has come up that for a number of faculty is a sticking point. I fully realize that you do not want to make any changes in the protocol but I would like you to hear this issue out. I believe that people are comfortable with the overall scope and importance of the study, and realize it will be a challenge. The issue that is causing concern is the stipulation of the use of surfactant up to 48 hours of age for infants in the treatment arm that are intubated in the NICU. The practice in Dallas is too treat with surfactant based upon clinical and CXR appearance eg., an infant intubated at 24 hours of age for apnea or atelectasis etc without a CXR appearance consistent with HMD does not get surfactant. Walid made sure to make the faculty aware that the overall use of surfactant in the network is 80% as cited on page 16 and with the intervention it was unclear if this would stay the same, or go in either direction. According to the division data base only 65% of infants with an OB EGA < 28 wks get surfactant in Dallas. Thus this group is at the low end of surfactant use for the network. I think this stipulation is concerning to the faculty since I could not cite any data on the efficacy of a blanket approach to administering surfactant without CXR findings past the first few hours of life. Thus if the protocol is to be as evidenced based as possible, the use of surfactant past the first few hours should have some caveats to it (attending preference, CXR consistent with HMD etc). I think, but do not know, that there would be much better buy in at this site if this issue was addressed. Let me know, Abbot

From: Petrie, Carolyn
To: Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; "M. D. Avroy A. Fanaroff (aaf2@cwru.edu)"; "M. D. Ed Donovan (edward.donovan@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)"
Cc: "Diane Timmer (Cincinnati) (diane.timmer@cchmc.org)"; " (Estelle.Fischer@cchmc.org)"; "Heidi Squibb (UCSD) (hsquibb@ucsd.edu)"; "Marsha Sumner (UAB) (msumner@peds.uab.edu)"; " (mlg@cwru.edu)"; Hastings, Betty J.
Subject: RE: DRCPAP conference call Thur. Feb 5 12-1pm EST (9-10am PST)
Date: Thursday, February 05, 2004 9:47:02 AM

Reminder for the call today:

The DRCPAP conference call to discuss the randomization is scheduled for
TODAY:
Thursday, February 5
12-1pm EST (9-10am PST)

If you are able to join, please dial tollfree
(b) (6) Passcode: (b) (6)

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:
Date: Monday, February 02, 2004 1:41:54 PM

Sure - I haven't heard a word.
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: 'Neil Finer'
Sent: Monday, February 02, 2004 9:08 AM
Subject: RE:

Neil
I'll have Carolyn set up a call.
On another note, can I share the DR CPAP manuscript that was submitted to Pediatrics with Dr. Berberich at NHLBI?
Thanks
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, February 02, 2004 11:42 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re:

Sure. We need to include Ken obviously. I assume it would be the Vent Committee. Can we do this week? I would be OK for Thursday around 9:00AM, 12:00 Eastern.
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Cc: 'petrie@rti.org'
Sent: Monday, February 02, 2004 5:13 AM
Subject: FW:

Neil
How would you like to proceed with a randomization strategy for the multiples - should we set up a call??
Thanks
Rose
-----Original Message-----
From: Poole, W. Kenneth [mailto:poo@rti.org]
Sent: Friday, January 30, 2004 4:13 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE:

We can do this but we need to remember that it affects much more than power. The other points I made in the e-mail concern me more than power and I wonder how much this will actually affect the consent rate. I have never done a trial by randomizing families and I'm not aware of any Network studies that have been randomized that way.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 30, 2004 3:42 PM

To: 'poo@rti.org'
Subject:

Ken
Neil would like you to do a power calculation for DR CPAP to determine how enrollment is affected if all individual sets of multiples are randomized to the same treatment group. Can you do this? many parents want their children to get the same treatment. It apparently has been done in other studies.
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:	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. 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); William Oh2 (WOh@wihri.org); Michele Walsh (mcw3@cwru.edu); Das, Abhik
Cc:	Higgins, Rosemary (NIH/NICHD); M. D. Neil Finer (nfiner@ucsd.edu); Hastings, Betty J.; Petrie, Carolyn
Subject:	COT Trial Jan 20 04
Date:	Wednesday, January 21, 2004 9:44:25 AM
Attachments:	COT Trial Jan 20 04.doc Summary- External Reviews and responses Jan 04.doc

Dear NRN Steering Committee-

Please find the updated COT Trial protocol and responses to external reviews, attached.

Thank you,
Carolyn

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 (±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 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 ≥ 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 (≤ 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 ≥ 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 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).

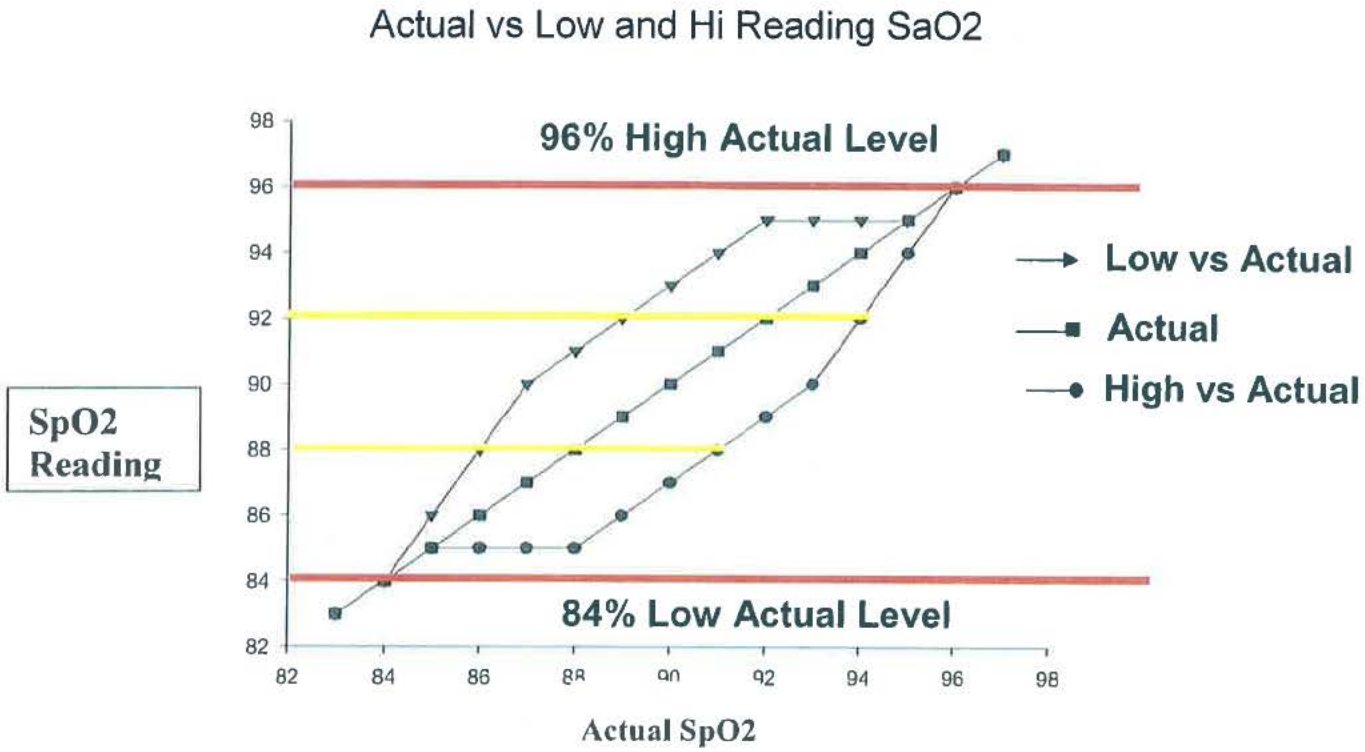
Table. Output and Actual SpO2 Targets and Alarms

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 ≥ 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

but it seems to me you will need to address PCO2 levels - both background/previous studies We have separated but I believe that there is a wish to monitor more closely or set tighter limits
PDA management/???Nitric Oxide??/feeding approaches/Vit A etc. We want to leave as amny areas as possible to current management. We are looking at a change on survival without BPD against current rates.
"MUST EXTUBATE" limit be that neonatologists will just be slower to wean babies down to that level??? This may require that we tighten up the extubation criteria and in view of current trend
Again, it's been a long time for me, but a rate of 15-20 bpm seems a bit high to go straight to extubation from.

1. I am a little surprised that the Network is using a "physiologic definition" of BPD, rather than their previously published definitions of mild moderate and severe BPD. Although unstated, I hope that the percentage of time spent in a hypocarbic or hypercarbic state is quantified. Will the duration of CPAP use be a secondary outcome? Since CPAP can cause abdominal distention, will enteral feeding tolerance/intolerance and growth be determined? Not an issue – Physiologic is accepted by Network. We have data on hypocarbia from Benchmarking – Do we want to collect.
2. , I would not have included infants > 26 6/7 weeks gestation, since success with CPAP (at our institution) is almost assured after that gestational age. It may be reasonable to exclude infants at 23 weeks gestation; however, a substantial portion of those infants can also be managed *without intubation and surfactant.* This is Columbia – The Network has not found this as almost all such infants are intubated.
3. I would not routinely use surfactant in infants who are 24-25 weeks gestation. The vast majority of those infants can be managed without intubation and surfactant. The use of intubation and positive pressure ventilation in the delivery room (or shortly afterward) adds a confounding variable. The IFDAS trial did not demonstrate a benefit to that strategy. This is Columbia – The Network has not found this as almost all such infants are intubated.
4.
5. The criteria for re-intubation of infants of 24-25 weeks gestation may be too conservative. We would routinely use a higher FiO_2. Furthermore, when bubble CPAP is used with nasal prongs, there are many reasons for CO_2 retention other than respiratory failure. In our experience, the most common reason for retention of carbon dioxide is nasal obstruction from secretions. In that regard, will be there be an educational program for nurses in the correct management of infants on prongs? A demonstration video and brief site visit does not seem sufficient. In the first few days of life, the use of nasal prongs is much more labor intensive than caring for infants who are intubated. This is Columbia – The Network has not found this as almost all such infants are intubated.

6. The use of the Neopuff device to provide CPAP in the delivery room may not be ideal and adds another variable. We routinely start bubble CPAP in the delivery room. Although a choice is given in the protocol, I would standardize the method for delivering CPAP prior to the NICU admission. This is Columbia – The

Network has not found this as almost all such infants are intubated. We believe that any form of CPAP may work, there is no data that bubble is better and we do not want to change practice to that extent.

7. Will permissive hypercapnia be part of the ventilatory strategy of infants who are intubated? If not, the comparisons with the "CPAP group" may be invalid. We have clearly indicated that a higher PCO2 will be a part of the strategy for the Treatment group.
8. It looks as if infants who are 26-27 weeks gestation will be managed with either Nasal SIMV or nasal CPAP. Is the nasal SIMV only for infants who have been intubated in the delivery room? There are not convincing data to use it as the initial mode of respiratory support. This is true but we may want to test as a part of a non-invasive strategy. The Network is using to some extent - Yale
9. The criteria for intubation/re-intubation of infants who are 26-27 weeks gestation are too liberal. Almost all infants who are initially treated with CPAP go through a transition phase after birth where their oxygen requirements may be quite high and carbon dioxide levels may exceed 65 torr. Sufficient time must be allowed for these infants to improve postnatally, otherwise the rate of intubation will be artificially high in this study. This is Columbia Here are the criteria:

An FiO_2 >.50 to maintain an indicated SpO2 ≥ 90% (using the altered Pulse Oximeters)

An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) The Network is unlikely to accept more sever criteria. We are not trying to test Columbias approach but rather early extubation after surf in the 24-25 wks group and CPAP vs surf in the larger group.

10. I am not sure why CPAP is being discontinued in infants without an oxygen requirement for one hour. Although is has not been validated, we leave our infants on room air-CPAP until about 32 weeks gestation. When applied correctly, the use of CPAP for a longer duration has no detectable morbidity and CPAP may decrease the incidence of severe apnea and bradycardia (and may avoid re-intubation). This is Columbia. We don't need to insist on removal of CPAP. We can change this to may remove.
11. Will the mouth be gently closed for infants receiving CPAP? (With respect to Dr. Morley, 7-8 mmHg CPAP is not needed if the mouth is gently closed or a nipple is kept there). The pressure might be increased to that level if the infant is failing CPAP. This is Columbia. We can add that this would be a good additional practice

    a. My biggest concern with this trial has to do with training of nursery staff. The "secret" for successful use of bubble CPAP is a nursing-staff who has been trained to deal with the subtleties of CPAP care. I would offer the nursery at Columbia as a potential training site. I am also concerned that the investigators at each site may be too quick to intubate or reintubate study infants, because they are not aware of the "natural history" of RDS in infants stabilized with CPAP shortly after birth.

b. My second concern has to do with the routine use of surfactant in study infants. The use of surfactant in intubated infants is clearly indicated. However, if one of the purposes of the study is to emulate the "Columbia Approach", then it fails to do so with the liberal use of intubation and surfactant. As noted above, we believe that a great many infants in this protocol will receive surfactant unnecessarily.

c. The investigators should try to reduce the amount of extraneous variability as much as possible. The key areas involve the use of positive pressure at delivery in the CPAP group instead of just putting the baby directly on CPAP, the use of surfactant in a CPAP treatment stratum, the lack of standardization of CPAP delivery and application, and the use of SIMV CPAP as a primary mode of CPAP ventilation. Too much extraneous variability may mask the treatment effects. It will be difficult enough to deal with the variability among centers. Trying to stratify for these things in the analysis may not work because so much power will be lost. This is Columbia

The outcome measures chosen are conventional in this area. One could argue that the primary outcome chosen for this intervention (death or severe ROP) is less important than the secondary outcome death or long-term impairment at 18 months. This is particularly relevant since the burden of long-term illness from retinopathy is far less than that from neurodevelopmental impairment, particularly cognitive delay. We agree and are being pragmatic and powering for both!!

To convince clinicians to use a given saturation range based on data on ROP only would be met with some suspicion if the direction of effect went in the opposite direction for neurodevelopmental outcome. Little detail is provided regarding the assessment of long-term impairment – how will it be defined, who will be performing the assessment, what measurement tools will be used. Already protocolized by Network!!These comments apply equally to the CPAP study.

. For instance if units place emphasis on arterial pO_2 above that of oxygen saturations this may lead to a convergence of oxygenation levels in the two groups making it very difficult to determine a difference in outcomes. Not likely – Who uses PaO2 not a continuous measure at bedside!!

demonstration of feasibility in the real world of the NICU and more detail on the important outcomes would strengthen this proposal. The unknown factor is how the pendulum of public opinion will swing as the trial progresses in the face of an accumulation of cohort data supporting a lower range of saturations. Do it now or not at all!!

It takes some time and effort to sort out what interventions are being compared in the CPAP section of the trial. The statement in the primary hypothesis that the 2 groups being compared are those managed with surfactant and conventional ventilation versus the use of early CPAP and permissive ventilatory strategy lacks detail and is inaccurate when compared to later statements. We can clarify but the Network has received the protocol and Flow diagrams!!

some, perhaps many babies will not be able to be recruited if the interval between admission and delivery is short. These babies will be systematically different from those recruited in several ways, perhaps most importantly in the rates of antenatal steroid usage. The mention of the criterion of unavailability of study personnel and apparatus

In section 3.9 it is stated that the applicants are planning for 15% attrition. This seems much too high and raises concerns about the applicability of the results obtained. Tin and Doyle have published independently about the results of inadequate followup rates and both found that those lost to followup or potentially lost were different to those who attended. Recent multicentered neonatal trials have aimed for and achieved followup rates well in excess of 90% and this has become the internationally accepted standard. requires further explanation. Not a feasible target in the Network!

For the 24-25 weekers, all will be intubated in the delivery room and receive prophylactic surfactant. The comparison being made in this stratum is not CPAP vs conventional ventilation but 2 different and somewhat idiosyncratic sets of extubation criteria. Considerable flexibility is allowed the clinician in determining whether babies in either group are suitable for extubation. For example, treatment group infants may not be extubated if they do not have a stable blood pressure, inadequate perfusion or require pressor or inotrope support. The first 2 parameters could be objectively defined but are not in this protocol. The third, the use of either pressors or fluids is an arbitrary decision made by the clinician unblinded to the group of allocation and therefore subject to bias. All is arbitrary, we can either define or not was done at the suggestion of some centers

Management of the more mature stratum is also difficult to follow in spite of the fact that the protocol repeats a section regarding the delivery room management! It is unclear what the criteria are for endotracheal intubation of these babies in the delivery room and it seems possible that infants in the treatment group may be intubated if the clinician is so inclined and control infants may not be intubated again according to physician preference. Once intubated, treatment infants must be extubated within 24 hours provided they meet all listed criteria. Again clinician preference could determine that these infants are managed with an endotracheal tube for longer – hemodynamically stable is a loose term which may be interpreted differently by different clinicians. It appears that if the clinician elects not to wean a baby below 20 breaths per minute, that baby may not be extubated. Therefore the stated aim that the purpose of the extubation criteria is to "minimize the duration of intubation of Treatment infants" may be thwarted.
We initially wanted prophylactic surf for all Control 26-27 weekers. Some centers said they don't do this. Overall the Network uses Surf 80% of the time – We will revert to Prophylactic Surf for all Controls as most stringent test for CPAP!!

My interpretation is that provided that the oxygen requirement does not rise above 30% the baby may be managed on NCPAP. In my experience many infants may be managed along these lines without requiring intubation and the statement that the protocol "forces the use of prophylactic surfactant for all control infants" may not prove to be correct – again depending on physician preferences. See above, Done for other centers

At one point they nominate a level of 5-6 cm water but in the final section 10.1 they suggest that 7-8 cm is the minimum that is likely to be effective. This discrepancy should be resolved. Along the same lines NIPPV is mentioned and it is suggested that it will be widely used throughout the study but no guidelines on PEEP levels, rates, peak pressures or inspiratory times are given. We will use 5 and allow increase to 7-8

No mention is made of an external monitoring committee in this protocol. Clearly such a committee will be needed to regularly review the results of the trial and the applicants may wish to specify important outcomes that may be monitored and consider circumstances under which recruitment might be halted. Routine

The applicants may wish to revise the following sections. Sec 4.4 "Serious and unanticipated adverse events may be anticipated in this vulnerable population". Page 12 "Intubation may be attempted if any of the following..." To paraphrase the words of a popular cultural figure "Do or do not. There is no attempt". Thanks

Survival without BPD is a laudable primary outcome measure, but it must be clearly defined and involve a physiologic measurement. "Early CPAP and a permissive *ventilator* strategy" sounds oxymoronic. Done

Will all IRBs approve studies for which parental consent is requested *prior to the birth of the infant?* My IRB has been very equivocal about this in the past. Yes
in Control infants, who *may* receive surfactant prophylactically if >26 weeks. Also, the surfactant preparations used are not standardized. We agree this was a compromise

The use of capillary blood gases is fraught with hazard in these infants, particularly if they are poorly perfused. What is a *stable* blood pressure, and what *normal* values will be used? There may be significant numbers of extubation failures if hypercapnia is present prior to attempted extubation. Moreover, given the variability of clinical practices, the leeway afforded in this study is a significant threat to valid results. Criteria for repeated doses of surfactant should be explicitly specified, and if possible, include pulmonary mechanics measurements. Will indicate that surf can be given if FiO2 > .30 at the usual redosing interval for that surfactant. The type or application of CPAP does not appear to be standardized (i.e., nasal prongs v cannula; fluidic, bubble, or other; level of pressure, etc.). Ventilator management in the "control" group is similarly not standardized [e.g., mode of ventilation (IMV, SIMV, or assist/control); form of ventilation (conventional/tidal or high frequency); method of ventilation (pressure-limited, pressure control, or volume-targeted); or style We are not controlling these – We do not want to study different ventilators etc.

The use of methylxanthines prior to extubation is not standardized and could impact the number of infants requiring reintubation. We have left to the individual centers

A flow diagram would be very helpful in understanding this study, especially since there are so many variations and outs. By that I mean that there are not just two possibilities:

high and low oxygen and CPAP or no CPAP. There are many other times that the protocol can vary. Already sent to all centers.

in the delivery room people are allowed to use whatever oxygen they want, they can use different types of ventilating devices for resuscitation. The devices are not described. Are these devices the same or are they different? Do they actually function the same and really produce the same pressures? Do some of them cause unintended higher or lower pressures? Is the PEEP/CPAP measurement accurate with each device? Unintended injury may be caused to the lung during resuscitation that will prevent the authors from determining if the injury was caused or prevented by oxygen, CPAP/PEEP or some other factor. Another weakness is the fact that there are not definite endpoints to many things. There is no data that any form of CPAP is different at present.

For instance, why are there endpoints for $PaCO_2$ of 55-60 mm Hg rather than one value, e.g., 60 mm HG? They also allow the use of higher inspired oxygen and carbon dioxide levels before intubatubating and extubating the trachea of some babies if the physicians desire to do so. Extubation criteria allow physicians to continue to ventilate patients who meet criteria for extubation if the patients are in the control group. This is up to the physicians. Ranges of 15 – 20 breaths per minute are used for extubation. Why not choose one number? All infants in the 24 – 25 week group will receive surfactant. Some of the 26 – 27 week infants will receive surfactant at the discretion of the physicians and under some circumstances must receive surfactant. Thus, many patients in the control group may receive surfactant. The investigators do not tell us from their preliminary data how many of the control group received surfactant in the delivery room. We have indicated that 80% of 26-27 weekers get surf in the Network and that number is > 90% < 26 weeks. We have removed the PaCO2 range

The preliminary data did not address the question of what to do with them. They constitute another group. In the delivery room the larger babies can be treated with CPAP or PEEP at the discretion of those doing the resuscitation. Again, this leads to several groups that differ from the smaller group of patients. In the ICN, the larger patients can be treated with nasal CPAP or nasal SIMV. Who decides which is to be used? What are the criteria for using one or the other? The authors point out that NSIMV appears to be more effective in small neonates, why not use that in all patients? The issue of NSIMV is real- many centers do not have the Star and thus NSIMV is not possible – Do we use NIMV? Or do we use CPAP only. This may result in more failures esp < 26 weeks. The alternative won't work. Do we allow either/or. If so the Control infants can also receive after extubation as well.

a. . If the blood gases they obtain include oxygen saturation values, the oxygenation portion of the study will be unmasked. Since the physicians will be allowed to use any concentration of oxygen they desire in the delivery room, how will this affect the outcomes? Would it not be possible to assign one of the saturation monitors used in the study and apply that monitor in the delivery room? They admit that they do not know how much oxygen is required and for how long to cause retinal

injury or lung disease. Having higher oxygen saturations for an hour or so during resuscitation may already have caused the injury and what they do afterwards may have no effect. We can take the PO to the DR and begin this part in the DR. We thought that allowing an hour would reduce the stress on the research personnel. It would be relatively simple to take the PO to the DR. Many centers do not use in the DR This would require a change in practice for many centers and I suspect would become a problem. I would suggest that we begin at 1 hour in the NICU. I doubt that 1 hour with the slight SpO2 differences will be relevant!

b. Will a person at each institution who is expert in developmental testing and a neurologist versed in developmental neurology be involved? There must be more information. What tests will be done? The investigators expect to lose 60 percent of the patients due to death and attrition. With all of the above groups, will they have enough patients to determine a difference between groups? This point is not discussed sufficiently.

The study should be reviewed by an NIH statistician who can address these questions. These are both already included!!

I have gone over the protocol again. Obviously this study addresses issues that are extremely important!! - HOWEVER - I continue to believe that it attempts to examine too many issues - and we will not have definitive answers to any of the questions when it's done:
- the feasibility study did not suggest at all that withholding surfactant was going to be a good idea - I am concerned about the ethics -of withholding surfactant treatment - when it has so clearly been demonstrated to be useful - how does one honestly write that consent form?
- seems to me you are comparing early CPAP, lack of surfactant, permissive hypercapnea,different ranges of Oxygen saturation - and different criteria for general management - i think this is too much - to look at
- the protocol is quite complex - and indeed - confusing - who is going to make sure all these rules are followed - it looks incredibly labor intensive to me!!!
- there are some other therapies that need clinical guidelines for management - including Rx of PDA - use of Pressors and certainly (the overpopular) hydrocortisone for blood pressure - and what is normal BP anyway?
- will the use of iNO be permitted? - and under what circumstances?
- some issues might be dealt with as Deviations from Clinical Guidelines =- rather than Protocol Violations

I congratulate everyone for their hard work - but feel that this needs to be focused - and made more practical

Page 13, 'subsequent intubation criteria for treatment infants' -- will need to do a good job of oeprationalizing 'hemodynamic instability' to try to keep a reasonably reproducible definition of 'hemodynamic instability unrepsonsive to volume and pharmacologic support.' I suppose some folks may be more aggressive than others in support before throwing in the towel and intubating

page 16, control infant protocol, nicu management -24-25 week strata. Is it reasonable to require a minimum 48 hour initial intubation? Should an attending be allowed to extubate in infant earlier if it's doing well, or is it so uncommon in a child that immature that we don't need to worry about requiring at least 48 hours?

page 17, bottom 'must be intubated if they meet any of these criteria.. I'll leave this to you, but is an fiO2 >.3 a conservative, aggressive, or mid-range indication to intubate and give surfactant?

page 18, mid-page 'extubation criteria for control 26-27 week infants. "must be attempted if ANY of these are present" Is that too aggressive? How about a baby that's not hard to ventilate (meets 1 or more of those) but just won't breathe on its own? Is that common?

Another review
It is obviously a very
important question to answer and after reading the protocl several times, the design and study power certainly seem valid. In summary, I have no significant changes to suggest and I am supportive of this protocol.

1) The description of the interventions is confusing. For instance, it is not clear to me why the desccription of delivery room management of the "treatment " group requires only one sentence (top of page 13) for 24-25 wk infants, but needs 6 paragraphs for 26-27 week infants. This is a complicated protocol making it especially important to present it as clearly as possible for the many people who will be involved. It would be a help if it could be simplified some, leaving a little more to clinical judgment.
2) For the pulse oximeter part of the study it is clearly very important that the altered oximeters be highly dependable to function properly. Presumably the evidence for this is in hand.
3) Dr. Ballard has raised two very important and related issues. First is whether the witholding of surfactant is ethically justifiable. I am not the right person to judge that, but clearly there must be a preponderance of opinion that there is equipoise between the two treament arms for the trial to go ahead. The second is that the CPAP arm is really CPAP and no surfactant vs intubation with surfactant, so it will not be possible to distinguish the role of CPAP from that of surfactant. CPAP might work, but its advantage might be missed because surfactant is witheld. Based on the literature review, it appears that the investigators have accepted this limitation because intubation and surfactant are linked. Presumably the Boston-Columbia comparison that they cite and other literature suggests the benefit of the proposed experimental therapy.

In summary, as a non-neonatologist I can see no clear reason why the study should not be approved. I suspect that the practicing neonatologists will knock the rough edges off the protocol, or if not, off the study disciplinarians. This may not be too disastrous as long as the data center is able to monitor that a substantial difference in CPAP and intubation is achieved between the groups. Centers not achieving a reasonable average difference should be brought up to snuff or dropped.

Hope this is helpful.

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: COT Trial
Date: Wednesday, January 14, 2004 3:27:58 PM

Hi Rose
I have been traveling. I am fine with sending out the critiques. This must be the most critiqued study ever devised. I fear that these will be reviewed and lead to more objections. Do you also want our responses?
I would rather sent out the revised protocol with the critiques and let the centers see how we responded. I will send that to you in the next 2-3 days. There are few changes from the last one I sent you apart from including the < 500gm infants.
Be well
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Sent: Monday, January 12, 2004 10:48 AM
Subject: COT Trial

Neil
Do you have an updated version of the COT Trial for the Steering Committee? In addition, some of the PIs have asked for the outside reviews, and in the spirit of openness, should be shared. Let me know when you want this to go to the Steering Committee.
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:	"Neil Finer "; "Poole, W. Kenneth "
Cc:	"Shahnaz Duara "; Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff, M.D. "; "Ed Donovan "
Subject:	RE: Fw:COT protocol
Date:	Tuesday, December 30, 2003 9:50:39 PM

A partial solution is to exclude 24 or even 25 weekers with prenatal evidence of growth retardation. We should also remember the effect of gender on survival, although it may seem discriminatory to exclude male infants.
Wally

-----Original Message-----
From: Neil Finer
To: Poole, W. Kenneth
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Sent: 12/30/2003 4:03 PM
Subject: Re: Fw:COT protocol

Thanks Ken
It sounds like we should go with a more standard randomization. The issue of
< 500 gm was that they would probably fail CPAP. I can live with including
them. I would ask for everyone's opinion.
Be well
Neil
----- Original Message -----
From: "Poole, W. Kenneth" <poo@rti.org>
To: <chenderson@ucsd.edu>; <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>; "Das, Abhik" <adas@rti.org>
Sent: Monday, December 29, 2003 5:15 AM
Subject: FW: Fw:COT protocol

> Neil/Chris,
>
>
>
> My thoughts:
>
> 1. If infants <500 gms. BW are unwittingly randomized into the study, I
> think they should be kept. Dropping them may not make that much difference
> in the outcome but it does violate the intent-to treat analysis strategy and
> would likely result in criticism of the study. 2. I see no way we can
> accommodate a dynamic randomization system to correct for imbalance that may
> be introduced by cluster randomization. If we randomize in clusters, we will
> have to live with the imbalance if it occurs. 3. If the randomization is
> done in clusters (e.g. by week)then the analysis of the data must take

this
> into consideration for the observations in a cluster can no longer be
> considered as statistically independent. This means that standard SAS
> programs (e.g. Logistic, GLM, etc.) are no longer appropriate. This
also
> means that the DRCPAP arm of the trial would have to be analyzed
separately
> from the O2 Sat arm since an observation cannot be treated as
clustered
and
> unclustered in the same analysis. Hence we basically have two
separate
> studies. There is also the consideration that sample sizes were
calculated
> assuming the DRCPAP arm would be randomized by infant. Cluster
> randomization will normally require a larger sample size.
>
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Monday, December 22, 2003 5:57 PM
> To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu;
> WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu
> Cc: Chris Henderson; wrich@ucsd.edu; Poole, W. Kenneth
> Subject: Re: Fw:COT protocol
>
>
> Hello Everyone
> By the numbers sent us, these infants represent about 5% of the 24
weekers.
> I have been giving the actual method of randomization considerable
thought.
> In view of the difficulties in randomizing at all hours of the day and
> night, the relative simplicity of the DR CPAP methodology, albeit the
> imbalance, should we reconsider a randomization by phone in to RTI
each
week
> by center for the CPAP vs Proph Surf? The PO would be separately
randomized
> on admission by the assignment of the actual oximeter. Would it be
possible
> for RTI to track enrollment every 100 infants and change the weekly
> allocation by center to ensure as little imbalance as possible? In
addition,
> this method automatically assigns all multiples to the same treatment,
this
> may more acceptable to parents. Ken, I would especially appreciate
your
> thoughts. Let me know what you think. Regards and best for the
Holidays
Neil
> ----- Original Message -----
> From: "Edward Donovan" <Edward.Donovan@cchmc.org>
> To: <higginsr@mail.nih.gov>; <sduara@miami.edu>;
<WCarlo@PEDS.UAB.EDU>;
> <aaf2@po.cwru.edu>; <nfiner@ucsd.edu>
> Sent: Monday, December 22, 2003 1:06 PM
> Subject: Re: Fw:COT protocol
>
>

> > We don't have the denominators, but my impression is that these
> > infants represent only 2-5% of the population at 24 and 25 weeks and
> > less at 26 and 27 weeks. This is small enough to ignore, but we
would
> > have a population based study if they are included. They will be
> > randomly distributed between treatment arms. I don't have a strong
> > preference but I lean toward including them.
> >
> > 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> 12/22/2003 10:55:43 AM >>>
> > Good Morning
> > Please review this. There appears to be 36 infants of 24-27 weeks
who
> > were less than 500 gm in the past year. This is a minimal estimate
as
> > the study will be based on best obstetrical estimate and some 23
> > weekers may be estimated at 24. Overall, I think that the exclusion
of
> > such infants is no
> > problem. On the other hand perhaps they ought to be left in for ease
> > of
> > simplicity. We will not know the weights till NICU admission, and
thus
> > would
> > have consented and done the DR maneuver. Please let me know your
> > thoughts.
> > Happy Holidays
> > Neil
> > ----- Original Message -----
> > From: "Das, Abhik" <adas@rti.org>
> > To: "'Neil Finer'" <nfiner@ucsd.edu>
> > Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole,
> > W.
> > Kenneth" <poo@rti.org>
> > Sent: Monday, December 22, 2003 6:26 AM
> > Subject: RE: protocol
> >
> >
> > > Please see attached.
> > > Thanks.
> > >
> > > Abhik
> > >
> > > -----Original Message-----
> > > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > > Sent: Friday, December 19, 2003 1:28 PM
> > > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> > > adas@rti.org
> > > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> > Wcarlo@peds.uab.edu;
> > > aaf2@po.cwru.edu

> > > Subject: Re: protocol
> > >
> > >
> > > Hello Everyone
> > > My thoughts would be that we enroll in the DR, and then remove
> > following
> > > weighing in the NICU. This shouldn't effect their care, and should
> > not
> > > create an imbalance. I would ask RTI to give us the actual number
of
> > infants
> > > in these week gestational age groups who weigh less than 500 gm.
We
> > would
> > > complete a DR form for all such infants, and that would allow us
to
> > track
> > > such infants using their GDB data. One thought would be to
continue
> > to
> > > collect all study data on such infants as this is a very
interesting
> > and
> > > problematic group. This would be a great secondary study. Ken, can
> > you get
> > > this information to us regarding the numbers of infants < 500gm in
> > each
> > > gestational week. Many thanks All the best over the Holidays and
New
> > Year.
> > > Neil
> > > ----- Original Message -----
> > > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> > <nfiner@ucsd.edu>;
> > > <poo@rti.org>; <adas@rti.org>
> > > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> > <Wcarlo@peds.uab.edu>;
> > > <aaf2@po.cwru.edu>
> > > Sent: Friday, December 19, 2003 7:52 AM
> > > Subject: RE: protocol
> > >
> > >
> > > > HI,
> > > > How about if RTI can give us the number of babies < 500 grams
from
> > the
> > > > previous analysis of number of babies by gestational age (24,
25,
> > 26,
> > > > 27)? How does "intent to treat" affect this study, i.e. a 24
week
> > 499
> > > > gram baby is born - is this child weighed prior to resuscitation
> > at
> > > > all centers or would we go with the "intent to treat"
> > consideration?
> > > > Maybe we should say estimated fetal weight of 500 grams or
greater

> > for
> > > > randomization prior to birth. This would be the "real life"
> > scenario.
> > > > There may be some < 500 gram infants that find their way into
the
> > > > study. Any thoughts from the statisticians also?
> > > >
> > > > Thanks for the thoughts.
> > > > Rose
> > > >
> > > > -----Original Message-----
> > > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > > Sent: Friday, December 19, 2003 10:42 AM
> > > > To: nfiner@ucsd.edu
> > > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> > Rosemary
> > > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> > aaf2@po.cwru.edu
> > > > Subject: protocol
> > > >
> > > >
> > > > Neil,
> > > > Sorry that I took so long to get back to you. I think that the
> > > > protocol is looking great! I found a couple of typos that I
fixed
> > > > with the Word "tracking changes" tool (attached). Have you
> > estimated
> > > > how many 24 and 25 weekers will be excluded given the 500 gram
> > cutoff?
> > > > Eventually we will want to describe the sealed envelop
> > randomization
> > > > method in more detail. How is stratification handled? What
> > happens
> > > > when the infant is <500g? How do we guarantee sequential
opening
> > of
> > > > envelops? How do we guarentee that only one envelop is opened
per
> > > > infant? Documenting date/time that envelop is opened? Etc. I
> > > > wonder if adjusting the pCO2 cutoff for venous gases is a
> > necessary
> > > > extra bit of complexity?
> > > > For treatment arm, 26-27 weeks, I thought the intubation
criteria
> > used
> > > > to be "may" rather than "must". In our place at present, we
would
> > > > certainly not intubate a baby with minimal resp. effort, sat 94,
> > good
> > > > gases and fiO2 0.55., but we will comply with the protocol. I
> > think
> > > > this will really increase the number of treatment infants
> > > > intubated
> > in
> > > > this strata. The goal for this group according to the protocol
is
> > to
> > > > "minimize the duration of intubation of Treatment infants".
> > Increasing
> > > > the fiO2 req. with the "must" statement would further "separate"

> > the
> > > > groups which external reviewers apparently wanted.
> > > > The protocol would certainly be simpler if it were a comparison
of
> > > > early management only, ie CPAP v proph. surf. But, I think want
> > we
> > > > wanted to test is a management strategy over the first weeks of
> > life.
> > > > "Separation" is an important issue, so I agree with the strategy
> > > > to
> > move
> > > > to "must" statements.
> > > > 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: Edward Donovan
To: aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc: mcw3@po.cwru.edu
Subject: RE: Fw:COT protocol
Date: Thursday, December 25, 2003 7:18:40 AM

I agree

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> 12/24/03 4:04 PM >>>
Because it is a MUST, I would use the lower CO2. Wally

-----Original Message-----
From: Neil Finer
To: "Ed Donovan ' '; "Avroy A. Fanaroff, M.D. ' '; "Shahnaz Duara '
';
"'Avroy A. Fanaroff' ' '; "Higgins, Rosemary (NIH/NICHD) ' '; Wally
Carlo,
M.D.
Cc: Michele Walsh-Sukys
Sent: 12/24/2003 2:03 PM
Subject: Re: Fw:COT protocol

Wally
Will centers accept a PaCO2 of < 45?? - I am comfortable with this.
Perhaps
50 is a compromise.
What do the rest of you think? We may be able to use control data from
benchmarking. Michele, could this be given to us??
Happy Holidays and New Year
Neil
----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
To: "'Neil Finer '" <nfiner@ucsd.edu>; ""Higgins, Rosemary (NIH/NICHD)
' '"
<higginsr@mail.nih.gov>; ""'Avroy A. Fanaroff' ' '" <aaf2@po.cwru.edu>;
""Shahnaz Duara ' '" <sduara@miami.edu>; ""'Avroy A. Fanaroff, M.D. '
'"
<aaf2@cwru.edu>; ""Ed Donovan ' '" <Edward.Donovan@chmcc.org>
Sent: Wednesday, December 24, 2003 5:56 AM
Subject: RE: Fw:COT protocol

> Neil et al.: The new change of MUST extubate the control group if the
PaCO2
> is <55 and pH is > 7.25 should be considered carefully this is not
standard
> practice. I like the MUST concept; my problem is with the targets for
the

> control group. I suspect these targets of CO2 and pH will lead to more
> agressive weaning than what is usual practice. Targets of <45 and pH
7.3
may
> be more in line of what people are practicing but a simple way to find
out
> is to collect these data for a week or so in 5 to 10 babies per
Network
site
> to know what is correct practice. This is how it was done for SAVE. We
> should aim the control group to be cared for as is the current Netwro
> practice. I am sure there will be variations in practice, but we
should
aim
> at the median practice and not an extreme for the control group. Wally
>
> -----Original Message-----
> From: Neil Finer
> To: Wally Carlo, M.D.; 'Higgins, Rosemary (NIH/NICHD) '; "Avroy A.
> Fanaroff' '; 'Shahnaz Duara '; 'Avroy A. Fanaroff, M.D. '; 'Ed Donovan
'
> Cc: poo@rti.org; adas@rti.org
> Sent: 12/23/2003 7:02 PM
> Subject: Re: Fw:COT protocol
>
> As we noted earlier, these infants represent 5% of the 24 weekers. I
> would
> ask that a DR sheet be completed for all infants randomized, and for
> those
> whose weight is < 500gm they be removed. RTI should be able to ensure
> that
> there is a balance in the site and strata randomization. Ken, would
this
> work??
> Be well
> Happy holidays
> Neil
> ----- Original Message -----
> From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
> To: "'Higgins, Rosemary (NIH/NICHD) '" <higginsr@mail.nih.gov>;
""Avroy
> A.
> Fanaroff' '" <aaf2@po.cwru.edu>; "'Neil Finer '" <nfiner@ucsd.edu>;
> "'Shahnaz Duara '" <sduara@miami.edu>; "'Neil Finer '"
> <nfiner@ucsd.edu>;
> "'Avroy A. Fanaroff, M.D. '" <aaf2@cwru.edu>; "'Ed Donovan '"
> <Edward.Donovan@chmcc.org>
> Cc: <poo@rti.org>; <adas@rti.org>
> Sent: Tuesday, December 23, 2003 11:44 AM
> Subject: RE: Fw:COT protocol
>
>
> > I believe the statisticians can handle this. The problem is that
> infants
> > are not weighed before resuscitation. Can we ask Ken? Wally
> >
> > -----Original Message-----
> > From: Higgins, Rosemary (NIH/NICHD)
> > To: 'Avroy A. Fanaroff'; Neil Finer; Wally Carlo, M.D.; Shahnaz
Duara;

> Neil
> > Finer; Avroy A. Fanaroff, M.D.; Ed Donovan
> > Cc: 'poo@rti.org'; 'adas@rti.org'
> > Sent: 12/23/2003 8:36 AM
> > Subject: RE: Fw:COT protocol
> >
> >
> > Av Raises excellent points regarding the < 500 gram infants. If they
> > are
> > excluded after randomization, how does this affect the numbers or
> > integrity
> > of the statistics for the study
> > -----Original Message-----
> > From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
> > Sent: Monday, December 22, 2003 6:04 PM
> > To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins,
> > Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
> > Subject: Re: Fw:COT protocol
> >
> >
> > Hi
> > Just returned from India
> > jet lagged and exhausted
> > Phenomenal experience
> > You take your life in your hands ever time you get in a car - have
> > never
> >
> > seen such chaos on the roads.
> > I think we should not include babies < 500 grams - the survival is so
> > dismal and the follow up equally so.
> > There are enough babies without these subjects and they only
> > complicate
> > the
> > issue in my opinion
> > Greetings and happy holidays to all
> > Av
> > At 07:55 AM 12/22/2003 -0800, Neil Finer wrote:
> > >Good Morning
> > >Please review this. There appears to be 36 infants of 24-27 weeks who
> > were
> > >less than 500 gm in the past year. This is a minimal estimate as the
> > study
> > >will be based on best obstetrical estimate and some 23 weekers may be
> > >estimated at 24. Overall, I think that the exclusion of such infants
> > is
> > no
> > >problem. On the other hand perhaps they ought to be left in for ease
> > of
> > >simplicity. We will not know the weights till NICU admission, and
> > thus
> > would
> > >have consented and done the DR maneuver. Please let me know your

> > thoughts.
> > >Happy Holidays
> > >Neil
> > >----- Original Message -----
> > >From: "Das, Abhik" <adas@rti.org>
> > >To: "'Neil Finer'" <nfiner@ucsd.edu>
> > >Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>;
"Poole,
> W.
> > >Kenneth" <poo@rti.org>
> > >Sent: Monday, December 22, 2003 6:26 AM
> > >Subject: RE: protocol
> > >
> > >
> > > > Please see attached.
> > > > Thanks.
> > > >
> > > > Abhik
> > > >
> > > > -----Original Message-----
> > > > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > > > Sent: Friday, December 19, 2003 1:28 PM
> > > > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan';
poo@rti.org;
> > > > adas@rti.org
> > > > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> > Wcarlo@peds.uab.edu;
> > > > aaf2@po.cwru.edu
> > > > Subject: Re: protocol
> > > >
> > > >
> > > > Hello Everyone
> > > > My thoughts would be that we enroll in the DR, and then remove
> > following
> > > > weighing in the NICU. This shouldn't effect their care, and
should
> > not
> > > > create an imbalance. I would ask RTI to give us the actual
number
> of
> > >infants
> > > > in these week gestational age groups who weigh less than 500 gm.
> We
> > would
> > > > complete a DR form for all such infants, and that would allow us
> to
> > track
> > > > such infants using their GDB data. One thought would be to
> continue
> > to
> > > > collect all study data on such infants as this is a very
> interesting
> > and
> > > > problematic group. This would be a great secondary study. Ken,
can
> > you
> > get
> > > > this information to us regarding the numbers of infants < 500gm
in
> > each

> > > > gestational week. Many thanks All the best over the Holidays and
> New
> > Year.
> > > > Neil
> > > > ----- Original Message -----
> > > > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > > > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> > <nfiner@ucsd.edu>;
> > > > <poo@rti.org>; <adas@rti.org>
> > > > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > > > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> > <Wcarlo@peds.uab.edu>;
> > > > <aaf2@po.cwru.edu>
> > > > Sent: Friday, December 19, 2003 7:52 AM
> > > > Subject: RE: protocol
> > > >
> > > >
> > > > > HI,
> > > > > How about if RTI can give us the number of babies < 500 grams
> from
> > the
> > > > > previous analysis of number of babies by gestational age (24,
> 25,
> > 26,
> > > > > 27)? How does "intent to treat" affect this study, i.e. a 24
> week
> > 499
> > > > > gram baby is born - is this child weighed prior to
resuscitation
> > at
> > > > > all centers or would we go with the "intent to treat"
> > consideration?
> > > > > Maybe we should say estimated fetal weight of 500 grams or
> greater
> > for
> > > > > randomization prior to birth. This would be the "real life"
> > scenario.
> > > > > There may be some < 500 gram infants that find their way into
> the
> > > > > study. Any thoughts from the statisticians also?
> > > > >
> > > > > Thanks for the thoughts.
> > > > > Rose
> > > > >
> > > > > -----Original Message-----
> > > > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > > > Sent: Friday, December 19, 2003 10:42 AM
> > > > > To: nfiner@ucsd.edu
> > > > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> > Rosemary
> > > > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> > aaf2@po.cwru.edu
> > > > > Subject: protocol
> > > > >
> > > > >
> > > > > Neil,
> > > > > Sorry that I took so long to get back to you. I think that
the
> > > > > protocol is looking great! I found a couple of typos that I
> fixed

> > > > > with the Word "tracking changes" tool (attached). Have you
> > estimated
> > > > > how many 24 and 25 weekers will be excluded given the 500 gram
> > cutoff?
> > > > > Eventually we will want to describe the sealed envelop
> > randomization
> > > > > method in more detail. How is stratification handled? What
> > happens
> > > > > when the infant is <500g? How do we guarantee sequential
> opening
> > of
> > > > > envelops? How do we guarentee that only one envelop is opened
> per
> > > > > infant? Documenting date/time that envelop is opened? Etc.
> > > > > I wonder if adjusting the pCO2 cutoff for venous gases is a
> > necessary
> > > > > extra bit of complexity?
> > > > > For treatment arm, 26-27 weeks, I thought the intubation
> criteria
> > used
> > > > > to be "may" rather than "must". In our place at present, we
> would
> > > > > certainly not intubate a baby with minimal resp. effort, sat
94,
> > good
> > > > > gases and fiO2 0.55., but we will comply with the protocol. I
> > think
> > > > > this will really increase the number of treatment infants
> > intubated in
> > > > > this strata. The goal for this group according to the
protocol
> is
> > to
> > > > > "minimize the duration of intubation of Treatment infants".
> > Increasing
> > > > > the fiO2 req. with the "must" statement would further
"separate"
> > the
> > > > > groups which external reviewers apparently wanted.
> > > > > The protocol would certainly be simpler if it were a
comparison
> of
> > > > > early management only, ie CPAP v proph. surf. But, I think
want
> > we
> > > > > wanted to test is a management strategy over the first weeks
of
> > life.
> > > > > "Separation" is an important issue, so I agree with the
strategy
> > to
> > move
> > > > > to "must" statements.
> > > > > 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 Fanaroff
To:	Wally Carlo, M.D.; "Neil Finer "; """Ed Donovan " " "; """Avroy A. Fanaroff, M.D. " " "; """Shahnaz Duara " " "; Higgins, Rosemary (NIH/NICHD)
Cc:	"Michele Walsh-Sukys "
Subject:	Re: Fw:COT protocol
Date:	Thursday, December 25, 2003 5:36:24 AM

Hi
Just intercepted Santa coming down the chimney
hppy holiday
Will defer to Michele
We are always in trouble when we come up with specific numbers for action,
but will have to reach a consensus and stick with it.
Regards
Av
I am in Florida hence this hokey E mail address

----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
To: "'Neil Finer '" <nfiner@ucsd.edu>; """Ed Donovan ' ' '"
<Edward.Donovan@chmcc.org>; """Avroy A. Fanaroff, M.D. ' ' '"
<aaf2@cwru.edu>; """Shahnaz Duara ' ' '" <sduara@miami.edu>; """Avroy A.
Fanaroff' ' '" <aaf2@cwru.edu>; """Higgins, Rosemary (NIH/NICHD) ' ' '"
<higginsr@mail.nih.gov>
Cc: "'Michele Walsh-Sukys '" <mcw3@cwru.edu>
Sent: Wednesday, December 24, 2003 4:09 PM
Subject: RE: Fw:COT protocol

> Because it is a MUST, I would use the lower CO2. Wally
>
> -----Original Message-----
> From: Neil Finer
> To: "Ed Donovan ' '; "Avroy A. Fanaroff, M.D. ' '; "Shahnaz Duara ' ';
> "'Avroy A. Fanaroff' ' '; "Higgins, Rosemary (NIH/NICHD) ' '; Wally
Carlo,
> M.D.
> Cc: Michele Walsh-Sukys
> Sent: 12/24/2003 2:03 PM
> Subject: Re: Fw:COT protocol
>
> Wally
> Will centers accept a PaCO2 of < 45?? - I am comfortable with this.
> Perhaps
> 50 is a compromise.
> What do the rest of you think? We may be able to use control data from
> benchmarking. Michele, could this be given to us??
> Happy Holidays and New Year
> Neil
> ----- Original Message -----
> From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
> To: "'Neil Finer '" <nfiner@ucsd.edu>; """Higgins, Rosemary (NIH/NICHD)
> ' '"
> <higginsr@mail.nih.gov>; """Avroy A. Fanaroff' ' '" <aaf2@po.cwru.edu>;
> "'Shahnaz Duara ' '" <sduara@miami.edu>; "'Avroy A. Fanaroff, M.D. '
> "'
> <aaf2@cwru.edu>; """Ed Donovan ' '" <Edward.Donovan@chmcc.org>

> Sent: Wednesday, December 24, 2003 5:56 AM
> Subject: RE: Fw:COT protocol
>
>
> > Neil et al.: The new change of MUST extubate the control group if the
> PaCO2
> > is <55 and pH is > 7.25 should be considered carefully this is not
> standard
> > practice. I like the MUST concept; my problem is with the targets for
> the
> > control group. I suspect these targets of CO2 and pH will lead to more
> > agressive weaning than what is usual practice. Targets of <45 and pH
> 7.3
> may
> > be more in line of what people are practicing but a simple way to find
> out
> > is to collect these data for a week or so in 5 to 10 babies per
> Network
> site
> > to know what is correct practice. This is how it was done for SAVE. We
> > should aim the control group to be cared for as is the current Netwro
> > practice. I am sure there will be variations in practice, but we
> should
> aim
> > at the median practice and not an extreme for the control group. Wally
> >
> > -----Original Message-----
> > From: Neil Finer
> > To: Wally Carlo, M.D.; 'Higgins, Rosemary (NIH/NICHD) '; "Avroy A.
> > Fanaroff' '; 'Shahnaz Duara '; 'Avroy A. Fanaroff, M.D. '; 'Ed Donovan
> '
> > Cc: poo@rti.org; adas@rti.org
> > Sent: 12/23/2003 7:02 PM
> > Subject: Re: Fw:COT protocol
> >
> > As we noted earlier, these infants represent 5% of the 24 weekers. I
> > would
> > ask that a DR sheet be completed for all infants randomized, and for
> > those
> > whose weight is < 500gm they be removed. RTI should be able to ensure
> > that
> > there is a balance in the site and strata randomization. Ken, would
> this
> > work??
> > Be well
> > Happy holidays
> > Neil
> > ----- Original Message -----
> > From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
> > To: "'Higgins, Rosemary (NIH/NICHD) '" <higginsr@mail.nih.gov>;
> ""Avroy
> > A.
> > Fanaroff' '" <aaf2@po.cwru.edu>; "'Neil Finer '" <nfiner@ucsd.edu>;
> > "'Shahnaz Duara '" <sduara@miami.edu>; "'Neil Finer '"
> > <nfiner@ucsd.edu>;
> > "'Avroy A. Fanaroff, M.D. '" <aaf2@cwru.edu>; "'Ed Donovan '"
> > <Edward.Donovan@chmcc.org>
> > Cc: <poo@rti.org>; <adas@rti.org>
> > Sent: Tuesday, December 23, 2003 11:44 AM
> > Subject: RE: Fw:COT protocol

> >
> >
> > > I believe the statisticians can handle this. The problem is that
> > infants
> > > are not weighed before resuscitation. Can we ask Ken? Wally
> > >
> > > -----Original Message-----
> > > From: Higgins, Rosemary (NIH/NICHD)
> > > To: 'Avroy A. Fanaroff'; Neil Finer; Wally Carlo, M.D.; Shahnaz
> Duara;
> > Neil
> > > Finer; Avroy A. Fanaroff, M.D.; Ed Donovan
> > > Cc: 'poo@rti.org'; 'adas@rti.org'
> > > Sent: 12/23/2003 8:36 AM
> > > Subject: RE: Fw:COT protocol
> > >
> > >
> > > Av Raises excellent points regarding the < 500 gram infants. If
> they
> > > are
> > > excluded after randomization, how does this affect the numbers or
> > > integrity
> > > of the statistics for the study
> > > -----Original Message-----
> > > From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
> > > Sent: Monday, December 22, 2003 6:04 PM
> > > To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer;
> Higgins,
> > > Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
> > > Subject: Re: Fw:COT protocol
> > >
> > >
> > > Hi
> > > Just returned from India
> > > jet lagged and exhausted
> > > Phenomenal experience
> > > You take your life in your hands ever time you get in a car - have
> > never
> > >
> > > seen such chaos on the roads.
> > > I think we should not include babies < 500 grams - the survival is
> so
> > > dismal and the follow up equally so.
> > > There are enough babies without these subjects and they only
> > complicate
> > > the
> > > issue in my opinion
> > > Greetings and happy holidays to all
> > > Av
> > > At 07:55 AM 12/22/2003 -0800, Neil Finer wrote:
> > > >Good Morning
> > > >Please review this. There appears to be 36 infants of 24-27 weeks
> who
> > > were
> > > >less than 500 gm in the past year. This is a minimal estimate as
> the
> > > study
> > > >will be based on best obstetrical estimate and some 23 weekers may
> be
> > > >estimated at 24. Overall, I think that the exclusion of such

> infants
> > is
> > > no
> > > >problem. On the other hand perhaps they ought to be left in for
> ease
> > of
> > > >simplicity. We will not know the weights till NICU admission, and
> > thus
> > > would
> > > >have consented and done the DR maneuver. Please let me know your
> > > thoughts.
> > > >Happy Holidays
> > > >Neil
> > > >----- Original Message -----
> > > >From: "Das, Abhik" <adas@rti.org>
> > > >To: "'Neil Finer'" <nfiner@ucsd.edu>
> > > >Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>;
> "Poole,
> > W.
> > > >Kenneth" <poo@rti.org>
> > > >Sent: Monday, December 22, 2003 6:26 AM
> > > >Subject: RE: protocol
> > > >
> > > >
> > > > > Please see attached.
> > > > > Thanks.
> > > > >
> > > > > Abhik
> > > > >
> > > > > -----Original Message-----
> > > > > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > > > > Sent: Friday, December 19, 2003 1:28 PM
> > > > > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan';
> poo@rti.org;
> > > > > adas@rti.org
> > > > > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> > > Wcarlo@peds.uab.edu;
> > > > > aaf2@po.cwru.edu
> > > > > Subject: Re: protocol
> > > > >
> > > > >
> > > > > Hello Everyone
> > > > > My thoughts would be that we enroll in the DR, and then remove
> > > following
> > > > > weighing in the NICU. This shouldn't effect their care, and
> should
> > > not
> > > > > create an imbalance. I would ask RTI to give us the actual
> number
> > of
> > > >infants
> > > > > in these week gestational age groups who weigh less than 500 gm.
> > We
> > > would
> > > > > complete a DR form for all such infants, and that would allow us
> > to
> > > track
> > > > > such infants using their GDB data. One thought would be to
> > continue
> > > to

> > > > > collect all study data on such infants as this is a very
> > interesting
> > > and
> > > > > problematic group. This would be a great secondary study. Ken,
> can
> > > you
> > > get
> > > > > this information to us regarding the numbers of infants < 500gm
> in
> > > each
> > > > > gestational week. Many thanks All the best over the Holidays and
> > New
> > > Year.
> > > > > Neil
> > > > > ----- Original Message -----
> > > > > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > > > > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> > > <nfiner@ucsd.edu>;
> > > > > <poo@rti.org>; <adas@rti.org>
> > > > > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > > > > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> > > <Wcarlo@peds.uab.edu>;
> > > > > <aaf2@po.cwru.edu>
> > > > > Sent: Friday, December 19, 2003 7:52 AM
> > > > > Subject: RE: protocol
> > > > >
> > > > >
> > > > > > HI,
> > > > > > How about if RTI can give us the number of babies < 500 grams
> > from
> > > the
> > > > > > previous analysis of number of babies by gestational age (24,
> > 25,
> > > 26,
> > > > > > 27)? How does "intent to treat" affect this study, i.e. a 24
> > week
> > > 499
> > > > > > gram baby is born - is this child weighed prior to
> resuscitation
> > > at
> > > > > > all centers or would we go with the "intent to treat"
> > > consideration?
> > > > > > Maybe we should say estimated fetal weight of 500 grams or
> > greater
> > > for
> > > > > > randomization prior to birth. This would be the "real life"
> > > scenario.
> > > > > > There may be some < 500 gram infants that find their way into
> > the
> > > > > > study. Any thoughts from the statisticians also?
> > > > > >
> > > > > > Thanks for the thoughts.
> > > > > > Rose
> > > > > >
> > > > > > -----Original Message-----
> > > > > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > > > > Sent: Friday, December 19, 2003 10:42 AM
> > > > > > To: nfiner@ucsd.edu
> > > > > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> > > Rosemary

> > > > > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> > > aaf2@po.cwru.edu
> > > > > > Subject: protocol
> > > > > >
> > > > > >
> > > > > > > Neil,
> > > > > > > Sorry that I took so long to get back to you. I think that
> the
> > > > > > > protocol is looking great! I found a couple of typos that I
> > fixed
> > > > > > > with the Word "tracking changes" tool (attached). Have you
> > > estimated
> > > > > > > how many 24 and 25 weekers will be excluded given the 500 gram
> > > cutoff?
> > > > > > > Eventually we will want to describe the sealed envelop
> > > randomization
> > > > > > > method in more detail. How is stratification handled? What
> > > happens
> > > > > > > when the infant is <500g? How do we guarantee sequential
> > opening
> > > of
> > > > > > > envelops? How do we guarentee that only one envelop is opened
> > per
> > > > > > > infant? Documenting date/time that envelop is opened? Etc.
> > > > > > > I wonder if adjusting the pCO2 cutoff for venous gases is a
> > > necessary
> > > > > > > extra bit of complexity?
> > > > > > > For treatment arm, 26-27 weeks, I thought the intubation
> > criteria
> > > used
> > > > > > > to be "may" rather than "must". In our place at present, we
> > would
> > > > > > > certainly not intubate a baby with minimal resp. effort, sat
> 94,
> > > good
> > > > > > > gases and fiO2 0.55., but we will comply with the protocol. I
> > > think
> > > > > > > this will really increase the number of treatment infants
> > > intubated in
> > > > > > > this strata. The goal for this group according to the
> protocol
> > is
> > > to
> > > > > > > "minimize the duration of intubation of Treatment infants".
> > > Increasing
> > > > > > > the fiO2 req. with the "must" statement would further
> "separate"
> > > the
> > > > > > > groups which external reviewers apparently wanted.
> > > > > > > The protocol would certainly be simpler if it were a
> comparison
> > of
> > > > > > > early management only, ie CPAP v proph. surf. But, I think
> want
> > > we
> > > > > > > wanted to test is a management strategy over the first weeks
> of
> > > life.
> > > > > > > "Separation" is an important issue, so I agree with the
> strategy

> > > to
> > > move
> > > > > > to "must" statements.
> > > > > > 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:	Neil Finer; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD); ""Avroy A. Fanaroff" "; "Shahnaz Duara "; "Avroy A. Fanaroff, M.D. "; "Ed Donovan "
Cc:	poo@rti.org; adas@rti.org
Subject:	Re: Fw:COT protocol
Date:	Wednesday, December 24, 2003 7:54:47 AM

Sounds like a plan
But then again we have had plans before
happy holidays
Av
At 05:02 PM 12/23/2003 -0800, Neil Finer wrote:
>As we noted earlier, these infants represent 5% of the 24 weekers. I would
>ask that a DR sheet be completed for all infants randomized, and for those
>whose weight is < 500gm they be removed. RTI should be able to ensure that
>there is a balance in the site and strata randomization. Ken, would this
>work??
>Be well
>Happy holidays
>Neil
>----- Original Message -----
>From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
>To: "'Higgins, Rosemary (NIH/NICHD) '" <higginsr@mail.nih.gov>; ""Avroy A.
>Fanaroff '" <aaf2@po.cwru.edu>; "'Neil Finer '" <nfiner@ucsd.edu>;
>"'Shahnaz Duara '" <sduara@miami.edu>; "'Neil Finer '" <nfiner@ucsd.edu>;
>"'Avroy A. Fanaroff, M.D. '" <aaf2@cwru.edu>; "'Ed Donovan '"
><Edward.Donovan@chmcc.org>
>Cc: <poo@rti.org>; <adas@rti.org>
>Sent: Tuesday, December 23, 2003 11:44 AM
>Subject: RE: Fw:COT protocol
>
>
> > I believe the statisticians can handle this. The problem is that infants
> > are not weighed before resuscitation. Can we ask Ken? Wally
> >
> > -----Original Message-----
> > From: Higgins, Rosemary (NIH/NICHD)
> > To: 'Avroy A. Fanaroff'; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara;
>Neil
> > Finer; Avroy A. Fanaroff, M.D.; Ed Donovan
> > Cc: 'poo@rti.org'; 'adas@rti.org'
> > Sent: 12/23/2003 8:36 AM
> > Subject: RE: Fw:COT protocol
> >
> >
> > Av Raises excellent points regarding the < 500 gram infants. If they
> > are
> > excluded after randomization, how does this affect the numbers or
> > integrity
> > of the statistics for the study
> > -----Original Message-----
> > From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
> > Sent: Monday, December 22, 2003 6:04 PM
> > To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins,
> > Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
> > Subject: Re: Fw:COT protocol
> >
> >

> > Hi
> > Just returned from India
> > jet lagged and exhausted
> > Phenomenal experience
> > You take your life in your hands ever time you get in a car - have never
> >
> > seen such chaos on the roads.
> > I think we should not include babies < 500 grams - the survival is so
> > dismal and the follow up equally so.
> > There are enough babies without these subjects and they only complicate
> > the
> > issue in my opinion
> > Greetings and happy holidays to all
> > Av
> > At 07:55 AM 12/22/2003 -0800, Neil Finer wrote:
> > >Good Morning
> > >Please review this. There appears to be 36 infants of 24-27 weeks who
> > were
> > >less than 500 gm in the past year. This is a minimal estimate as the
> > study
> > >will be based on best obstetrical estimate and some 23 weekers may be
> > >estimated at 24. Overall, I think that the exclusion of such infants is
> > no
> > >problem. On the other hand perhaps they ought to be left in for ease of
> > >simplicity. We will not know the weights till NICU admission, and thus
> > would
> > >have consented and done the DR maneuver. Please let me know your
> > thoughts.
> > >Happy Holidays
> > >Neil
> > >----- Original Message -----
> > >From: "Das, Abhik" <adas@rti.org>
> > >To: "'Neil Finer'" <nfiner@ucsd.edu>
> > >Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole, W.
> > >Kenneth" <poo@rti.org>
> > >Sent: Monday, December 22, 2003 6:26 AM
> > >Subject: RE: protocol
> > >
> > >
> > > > Please see attached.
> > > > Thanks.
> > > >
> > > > Abhik
> > > >
> > > > -----Original Message-----
> > > > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > > > Sent: Friday, December 19, 2003 1:28 PM
> > > > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> > > > adas@rti.org
> > > > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> > Wcarlo@peds.uab.edu;
> > > > aaf2@po.cwru.edu
> > > > Subject: Re: protocol
> > > >
> > > >
> > > > Hello Everyone
> > > > My thoughts would be that we enroll in the DR, and then remove
> > following
> > > > weighing in the NICU. This shouldn't effect their care, and should
> > not

> > > > create an imbalance. I would ask RTI to give us the actual number of
> > >infants
> > > > in these week gestational age groups who weigh less than 500 gm. We
> > would
> > > > complete a DR form for all such infants, and that would allow us to
> > track
> > > > such infants using their GDB data. One thought would be to continue
> > to
> > > > collect all study data on such infants as this is a very interesting
> > and
> > > > problematic group. This would be a great secondary study. Ken, can
> > you
> > get
> > > > this information to us regarding the numbers of infants < 500gm in
> > each
> > > > gestational week. Many thanks All the best over the Holidays and New
> > Year.
> > > > Neil
> > > > ----- Original Message -----
> > > > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > > > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> > <nfiner@ucsd.edu>;
> > > > <poo@rti.org>; <adas@rti.org>
> > > > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > > > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> > <Wcarlo@peds.uab.edu>;
> > > > <aaf2@po.cwru.edu>
> > > > Sent: Friday, December 19, 2003 7:52 AM
> > > > Subject: RE: protocol
> > > >
> > > >
> > > > > HI,
> > > > > How about if RTI can give us the number of babies < 500 grams from
> > the
> > > > > previous analysis of number of babies by gestational age (24, 25,
> > 26,
> > > > > 27)? How does "intent to treat" affect this study, i.e. a 24 week
> > 499
> > > > > gram baby is born - is this child weighed prior to resuscitation
> > at
> > > > > all centers or would we go with the "intent to treat"
> > consideration?
> > > > > Maybe we should say estimated fetal weight of 500 grams or greater
> > for
> > > > > randomization prior to birth. This would be the "real life"
> > scenario.
> > > > > There may be some < 500 gram infants that find their way into the
> > > > > study. Any thoughts from the statisticians also?
> > > > >
> > > > > Thanks for the thoughts.
> > > > > Rose
> > > > >
> > > > > -----Original Message-----
> > > > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > > > Sent: Friday, December 19, 2003 10:42 AM
> > > > > To: nfiner@ucsd.edu
> > > > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> > Rosemary
> > > > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> > aaf2@po.cwru.edu

> > > > > Subject: protocol
> > > > >
> > > > >
> > > > > Neil,
> > > > > Sorry that I took so long to get back to you. I think that the
> > > > > protocol is looking great! I found a couple of typos that I fixed
> > > > > with the Word "tracking changes" tool (attached). Have you
> > estimated
> > > > > how many 24 and 25 weekers will be excluded given the 500 gram
> > cutoff?
> > > > > Eventually we will want to describe the sealed envelop
> > randomization
> > > > > method in more detail. How is stratification handled? What
> > happens
> > > > > when the infant is <500g? How do we guarantee sequential opening
> > of
> > > > > envelops? How do we guarentee that only one envelop is opened per
> > > > > infant? Documenting date/time that envelop is opened? Etc.
> > > > > I wonder if adjusting the pCO2 cutoff for venous gases is a
> > necessary
> > > > > extra bit of complexity?
> > > > > For treatment arm, 26-27 weeks, I thought the intubation criteria
> > used
> > > > > to be "may" rather than "must". In our place at present, we would
> > > > > certainly not intubate a baby with minimal resp. effort, sat 94,
> > good
> > > > > gases and fiO2 0.55., but we will comply with the protocol. I
> > think
> > > > > this will really increase the number of treatment infants
> > intubated in
> > > > > this strata. The goal for this group according to the protocol is
> > to
> > > > > "minimize the duration of intubation of Treatment infants".
> > Increasing
> > > > > the fiO2 req. with the "must" statement would further "separate"
> > the
> > > > > groups which external reviewers apparently wanted.
> > > > > The protocol would certainly be simpler if it were a comparison of
> > > > > early management only, ie CPAP v proph. surf. But, I think want
> > we
> > > > > wanted to test is a management strategy over the first weeks of
> > life.
> > > > > "Separation" is an important issue, so I agree with the strategy
> > to
> > move
> > > > > to "must" statements.
> > > > > 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: Wally Carlo, M.D.
To: "Neil Finer "; "Edward Donovan "; Higgins, Rosemary (NIH/NICHD); "sduara@miami.edu "; "aaf2@po.cwru.edu "
Cc: "Chris Henderson "; "wrich@ucsd.edu "; "Poole, W. Kenneth "
Subject: RE: Fw:COT protocol
Date: Tuesday, December 23, 2003 2:31:35 PM

Neil: I think a phone randomization would be the best. Even the PO can be assigend by the RTI, if they are told the serial or other ID # of the available oximters. Wally

-----Original Message-----
From: Neil Finer
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu
Cc: Chris Henderson; wrich@ucsd.edu; Poole, W. Kenneth
Sent: 12/22/2003 4:56 PM
Subject: Re: Fw:COT protocol

Hello Everyone
By the numbers sent us, these infants represent about 5% of the 24 weekers.
I have been giving the actual method of randomization considerable thought.
In view of the difficulties in randomizing at all hours of the day and night, the relative simplicity of the DR CPAP methodology, albeit the imbalance, should we reconsider a randomization by phone in to RTI each week
by center for the CPAP vs Proph Surf? The PO would be separately randomized
on admission by the assignment of the actual oximeter.
Would it be possible for RTI to track enrollment every 100 infants and change the weekly allocation by center to ensure as little imbalance as possible? In addition, this method automatically assigns all multiples to
the same treatment, this may more acceptable to parents.
Ken, I would especially appreciate your thoughts.
Let me know what you think.
Regards and best for the Holidays
Neil
----- Original Message -----
From: "Edward Donovan" <Edward.Donovan@cchmc.org>
To: <higginsr@mail.nih.gov>; <sduara@miami.edu>; <WCarlo@PEDS.UAB.EDU>; <aaf2@po.cwru.edu>; <nfiner@ucsd.edu>
Sent: Monday, December 22, 2003 1:06 PM
Subject: Re: Fw:COT protocol

> We don't have the denominators, but my impression is that these infants
> represent only 2-5% of the population at 24 and 25 weeks and less at 26
> and 27 weeks. This is small enough to ignore, but we would have a
> population based study if they are included. They will be randomly
> distributed between treatment arms.
> I don't have a strong preference but I lean toward including them.
>
> 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> 12/22/2003 10:55:43 AM >>>
> Good Morning
> Please review this. There appears to be 36 infants of 24-27 weeks who
> were
> less than 500 gm in the past year. This is a minimal estimate as the
> study
> will be based on best obstetrical estimate and some 23 weekers may be
> estimated at 24. Overall, I think that the exclusion of such infants
is
> no
> problem. On the other hand perhaps they ought to be left in for ease
> of
> simplicity. We will not know the weights till NICU admission, and thus
> would
> have consented and done the DR maneuver. Please let me know your
> thoughts.
> Happy Holidays
> Neil
> ----- Original Message -----
> From: "Das, Abhik" <adas@rti.org>
> To: "'Neil Finer'" <nfiner@ucsd.edu>
> Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole,
> W.
> Kenneth" <poo@rti.org>
> Sent: Monday, December 22, 2003 6:26 AM
> Subject: RE: protocol
>
>
> > Please see attached.
> > Thanks.
> >
> > Abhik
> >
> > -----Original Message-----
> > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > Sent: Friday, December 19, 2003 1:28 PM
> > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> > adas@rti.org
> > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> Wcarlo@peds.uab.edu;
> > aaf2@po.cwru.edu
> > Subject: Re: protocol
> >
> >
> > Hello Everyone
> > My thoughts would be that we enroll in the DR, and then remove
> following
> > weighing in the NICU. This shouldn't effect their care, and should
> not
> > create an imbalance. I would ask RTI to give us the actual number of
> infants

> > in these week gestational age groups who weigh less than 500 gm. We
> would
> > complete a DR form for all such infants, and that would allow us to
> track
> > such infants using their GDB data. One thought would be to continue
> to
> > collect all study data on such infants as this is a very interesting
> and
> > problematic group. This would be a great secondary study. Ken, can
> you get
> > this information to us regarding the numbers of infants < 500gm in
> each
> > gestational week. Many thanks All the best over the Holidays and New
> Year.
> > Neil
> > ----- Original Message -----
> > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> <nfiner@ucsd.edu>;
> > <poo@rti.org>; <adas@rti.org>
> > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> <Wcarlo@peds.uab.edu>;
> > <aaf2@po.cwru.edu>
> > Sent: Friday, December 19, 2003 7:52 AM
> > Subject: RE: protocol
> >
> >
> > > HI,
> > > How about if RTI can give us the number of babies < 500 grams from
> the
> > > previous analysis of number of babies by gestational age (24, 25,
> 26,
> > > 27)? How does "intent to treat" affect this study, i.e. a 24 week
> 499
> > > gram baby is born - is this child weighed prior to resuscitation
> at
> > > all centers or would we go with the "intent to treat"
> consideration?
> > > Maybe we should say estimated fetal weight of 500 grams or greater
> for
> > > randomization prior to birth. This would be the "real life"
> scenario.
> > > There may be some < 500 gram infants that find their way into the
> > > study. Any thoughts from the statisticians also?
> > >
> > > Thanks for the thoughts.
> > > Rose
> > >
> > > -----Original Message-----
> > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > Sent: Friday, December 19, 2003 10:42 AM
> > > To: nfiner@ucsd.edu
> > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> Rosemary
> > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> aaf2@po.cwru.edu
> > > Subject: protocol
> > >
> > >

> > > Neil,
> > > Sorry that I took so long to get back to you. I think that the
> > > protocol is looking great! I found a couple of typos that I fixed
> > > with the Word "tracking changes" tool (attached). Have you
> estimated
> > > how many 24 and 25 weekers will be excluded given the 500 gram
> cutoff?
> > > Eventually we will want to describe the sealed envelop
> randomization
> > > method in more detail. How is stratification handled? What
> happens
> > > when the infant is <500g? How do we guarantee sequential opening
> of
> > > envelops? How do we guarentee that only one envelop is opened per
> > > infant? Documenting date/time that envelop is opened? Etc.
> > > I wonder if adjusting the pCO2 cutoff for venous gases is a
> necessary
> > > extra bit of complexity?
> > > For treatment arm, 26-27 weeks, I thought the intubation criteria
> used
> > > to be "may" rather than "must". In our place at present, we would
> > > certainly not intubate a baby with minimal resp. effort, sat 94,
> good
> > > gases and fiO2 0.55., but we will comply with the protocol. I
> think
> > > this will really increase the number of treatment infants
intubated
> in
> > > this strata. The goal for this group according to the protocol is
> to
> > > "minimize the duration of intubation of Treatment infants".
> Increasing
> > > the fiO2 req. with the "must" statement would further "separate"
> the
> > > groups which external reviewers apparently wanted.
> > > The protocol would certainly be simpler if it were a comparison of
> > > early management only, ie CPAP v proph. surf. But, I think want
> we
> > > wanted to test is a management strategy over the first weeks of
> life.
> > > "Separation" is an important issue, so I agree with the strategy
to
> move
> > > to "must" statements.
> > > 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: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Fw:COT protocol
Date: Tuesday, December 23, 2003 12:32:07 PM

Hi
Thanks for update
Lindda had called and mentioned that they thought that there were inconsistencies in the abstract and the text - there were not.
Evidently you sorted it all out
Thanks
Av
At 12:30 PM 12/23/2003, you wrote:
>Thanks
>Glad you arrived home safely.
>The nejm sent your paper uot for review
>
>Rose
>--------------------------
>Sent from my BlackBerry Wireless Handheld
>
>
>-----Original Message-----
>From: Avroy A. Fanaroff <aaf2@po.cwru.edu>
>To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>
>Sent: Tue Dec 23 12:16:00 2003
>Subject: Re: Fw:COT protocol
>
>Hi
>No problem
>Will contact him to see if he needs the power point slides
>Thanks and happy holidays
>Greetings
>Av
>
>
>At 11:19 AM 12/23/2003, you wrote:
> >Av
> >Unrelated
> >Alan Jobe would like to use the data in the gdb6 paper at the NICHD AAP
> >meeting in Jan. Is this ok??
> >Rose
> >--------------------------
> >Sent from my BlackBerry Wireless Handheld
> >
> >
> >-----Original Message-----
> >From: Avroy A. Fanaroff <aaf2@po.cwru.edu>
> >To: Neil Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@PEDS.UAB.EDU>;
> >Shahnaz Duara <sduara@miami.edu>; Neil Finer <nfiner@ucsd.edu>; Higgins,
> >Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>; Avroy A. Fanaroff, M.D.
> ><aaf2@cwru.edu>; Ed Donovan <Edward.Donovan@chmcc.org>
> >Sent: Mon Dec 22 18:04:19 2003
> >Subject: Re: Fw:COT protocol
> >
> >Hi
> >Just returned from India
> >jet lagged and exhausted

> >Phenomenal experience
> >You take your life in your hands ever time you get in a car - have never
> >seen such chaos on the roads.
> >I think we should not include babies < 500 grams - the survival is so
> >dismal and the follow up equally so.
> >There are enough babies without these subjects and they only complicate the
> >issue in my opinion
> >Greetings and happy holidays to all
> >Av
> >At 07:55 AM 12/22/2003 -0800, Neil Finer wrote:
> > >Good Morning
> > >Please review this. There appears to be 36 infants of 24-27 weeks who
>were
> > >less than 500 gm in the past year. This is a minimal estimate as the
>study
> > >will be based on best obstetrical estimate and some 23 weekers may be
> > >estimated at 24. Overall, I think that the exclusion of such infants is
>no
> > >problem. On the other hand perhaps they ought to be left in for ease of
> > >simplicity. We will not know the weights till NICU admission, and thus
> >would
> > >have consented and done the DR maneuver. Please let me know your
>thoughts.
> > >Happy Holidays
> > >Neil
> > >----- Original Message -----
> > >From: "Das, Abhik" <adas@rti.org>
> > >To: "'Neil Finer'" <nfiner@ucsd.edu>
> > >Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole, W.
> > >Kenneth" <poo@rti.org>
> > >Sent: Monday, December 22, 2003 6:26 AM
> > >Subject: RE: protocol
> > >
> > >
> > > > Please see attached.
> > > > Thanks.
> > > >
> > > > Abhik
> > > >
> > > > -----Original Message-----
> > > > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > > > Sent: Friday, December 19, 2003 1:28 PM
> > > > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> > > > adas@rti.org
> > > > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> >Wcarlo@peds.uab.edu;
> > > > aaf2@po.cwru.edu
> > > > Subject: Re: protocol
> > > >
> > > >
> > > > Hello Everyone
> > > > My thoughts would be that we enroll in the DR, and then remove
>following
> > > > weighing in the NICU. This shouldn't effect their care, and should not
> > > > create an imbalance. I would ask RTI to give us the actual number of
> > >infants
> > > > in these week gestational age groups who weigh less than 500 gm. We
> >would
> > > > complete a DR form for all such infants, and that would allow us to
> >track

> > > > such infants using their GDB data. One thought would be to continue to
> > > > collect all study data on such infants as this is a very interesting
>and
> > > > problematic group. This would be a great secondary study. Ken, can you
> >get
> > > > this information to us regarding the numbers of infants < 500gm in
>each
> > > > gestational week. Many thanks All the best over the Holidays and New
> >Year.
> > > > Neil
> > > > ----- Original Message -----
> > > > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > > > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>; <nfiner@ucsd.edu>;
> > > > <poo@rti.org>; <adas@rti.org>
> > > > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > > > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
><Wcarlo@peds.uab.edu>;
> > > > <aaf2@po.cwru.edu>
> > > > Sent: Friday, December 19, 2003 7:52 AM
> > > > Subject: RE: protocol
> > > >
> > > >
> > > > > HI,
> > > > > How about if RTI can give us the number of babies < 500 grams from
>the
> > > > > previous analysis of number of babies by gestational age (24, 25,
>26,
> > > > > 27)? How does "intent to treat" affect this study, i.e. a 24 week
>499
> > > > > gram baby is born - is this child weighed prior to resuscitation at
> > > > > all centers or would we go with the "intent to treat" consideration?
> > > > > Maybe we should say estimated fetal weight of 500 grams or greater
>for
> > > > > randomization prior to birth. This would be the "real life"
>scenario.
> > > > > There may be some < 500 gram infants that find their way into the
> > > > > study. Any thoughts from the statisticians also?
> > > > >
> > > > > Thanks for the thoughts.
> > > > > Rose
> > > > >
> > > > > -----Original Message-----
> > > > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > > > Sent: Friday, December 19, 2003 10:42 AM
> > > > > To: nfiner@ucsd.edu
> > > > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
>Rosemary
> > > > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu
> > > > > Subject: protocol
> > > > >
> > > > >
> > > > > Neil,
> > > > > Sorry that I took so long to get back to you. I think that the
> > > > > protocol is looking great! I found a couple of typos that I fixed
> > > > > with the Word "tracking changes" tool (attached). Have you estimated
> > > > > how many 24 and 25 weekers will be excluded given the 500 gram
>cutoff?
> > > > > Eventually we will want to describe the sealed envelop randomization
> > > > > method in more detail. How is stratification handled? What happens
> > > > > when the infant is <500g? How do we guarantee sequential opening of

> > > > > envelops? How do we guarentee that only one envelop is opened per
> > > > > infant? Documenting date/time that envelop is opened? Etc.
> > > > > I wonder if adjusting the pCO2 cutoff for venous gases is a
>necessary
> > > > > extra bit of complexity?
> > > > > For treatment arm, 26-27 weeks, I thought the intubation criteria
>used
> > > > > to be "may" rather than "must". In our place at present, we would
> > > > > certainly not intubate a baby with minimal resp. effort, sat 94,
>good
> > > > > gases and fiO2 0.55., but we will comply with the protocol. I think
> > > > > this will really increase the number of treatment infants intubated
>in
> > > > > this strata. The goal for this group according to the protocol is
>to
> > > > > "minimize the duration of intubation of Treatment infants".
> >Increasing
> > > > > the fiO2 req. with the "must" statement would further "separate" the
> > > > > groups which external reviewers apparently wanted.
> > > > > The protocol would certainly be simpler if it were a comparison of
> > > > > early management only, ie CPAP v proph. surf. But, I think want we
> > > > > wanted to test is a management strategy over the first weeks of
>life.
> > > > > "Separation" is an important issue, so I agree with the strategy to
> >move
> > > > > to "must" statements.
> > > > > 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
> > > >
> > > >
>
>Avroy A Fanaroff M.D.
>Interim Chair of Pediatrics
>RB and C Room 784
>11100 Euclid Avenue
>Cleveland, Ohio 44106-6003
>E mail aaf2@cwru.edu is changing to
>avroy.fanaroff@case.edu
>
>
>Phone 216-844-3884
>Fax 216-844-1479
>
>
>
>
> The enclosed information is STRICTLY CONFIDENTIAL and is intended for the
>use of the addressee only. University Hospitals Health System and its
>affiliates disclaim any responsibility for unauthorized disclosure of this
>information to anyone other than the addressee.
>

>Federal and Ohio law protect patient medical information disclosed in this
>email, including psychiatric disorders, (HIV) test results, AIDs-related
>conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42
>CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit
>disclosure of this information without the specific written consent of the
>person to whom it pertains, or as otherwise permitted by law.

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu is changing to
avroy.fanaroff@case.edu

Phone 216-844-3884
Fax 216-844-1479

From:	Edward Donovan
To:	Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc:	poo@rti.org; chenderson@ucsd.edu; wrich@ucsd.edu
Subject:	Re: Fw:COT protocol
Date:	Tuesday, December 23, 2003 11:39:44 AM

I think we should try to randomized each patient individually using the proposed stratification strategy. If we enroll antenatally, we could randomized asap after enrollment. The downside here is that caregivers know which ventilation group the patient is for some hours or some days prior to birth. I'm not sure that this is much of a 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

>>> "Neil Finer" <nfiner@ucsd.edu> 12/22/2003 5:56:30 PM >>>
Hello Everyone
By the numbers sent us, these infants represent about 5% of the 24 weekers.
I have been giving the actual method of randomization considerable thought.
In view of the difficulties in randomizing at all hours of the day and night, the relative simplicity of the DR CPAP methodology, albeit the imbalance, should we reconsider a randomization by phone in to RTI each week
by center for the CPAP vs Proph Surf? The PO would be separately randomized
on admission by the assignment of the actual oximeter.
Would it be possible for RTI to track enrollment every 100 infants and change the weekly allocation by center to ensure as little imbalance as
possible? In addition, this method automatically assigns all multiples to
the same treatment, this may more acceptable to parents.
Ken, I would especially appreciate your thoughts.
Let me know what you think.
Regards and best for the Holidays
Neil
----- Original Message -----
From: "Edward Donovan" <Edward.Donovan@cchmc.org>
To: <higginsr@mail.nih.gov>; <sduara@miami.edu>;
<WCarlo@PEDS.UAB.EDU>;
<aaf2@po.cwru.edu>; <nfiner@ucsd.edu>
Sent: Monday, December 22, 2003 1:06 PM
Subject: Re: Fw:COT protocol

> We don't have the denominators, but my impression is that these infants
> represent only 2-5% of the population at 24 and 25 weeks and less at

> and 27 weeks. This is small enough to ignore, but we would have a
> population based study if they are included. They will be randomly
> distributed between treatment arms.
> I don't have a strong preference but I lean toward including them.
>
> 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> 12/22/2003 10:55:43 AM >>>
> Good Morning
> Please review this. There appears to be 36 infants of 24-27 weeks
who
> were
> less than 500 gm in the past year. This is a minimal estimate as the
> study
> will be based on best obstetrical estimate and some 23 weekers may
be
> estimated at 24. Overall, I think that the exclusion of such infants
is
> no
> problem. On the other hand perhaps they ought to be left in for ease
> of
> simplicity. We will not know the weights till NICU admission, and
thus
> would
> have consented and done the DR maneuver. Please let me know your
> thoughts.
> Happy Holidays
> Neil
> ----- Original Message -----
> From: "Das, Abhik" <adas@rti.org>
> To: "'Neil Finer'" <nfiner@ucsd.edu>
> Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole,
> W.
> Kenneth" <poo@rti.org>
> Sent: Monday, December 22, 2003 6:26 AM
> Subject: RE: protocol
>
>
> > Please see attached.
> > Thanks.
> >
> > Abhik
> >
> > -----Original Message-----
> > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > Sent: Friday, December 19, 2003 1:28 PM
> > To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> > adas@rti.org
> > Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
> Wcarlo@peds.uab.edu;
> > aaf2@po.cwru.edu

> > Subject: Re: protocol
> >
> >
> > Hello Everyone
> > My thoughts would be that we enroll in the DR, and then remove
> following
> > weighing in the NICU. This shouldn't effect their care, and should
> not
> > create an imbalance. I would ask RTI to give us the actual number
of
> infants
> > in these week gestational age groups who weigh less than 500 gm.
We
> would
> > complete a DR form for all such infants, and that would allow us
to
> track
> > such infants using their GDB data. One thought would be to
continue
> to
> > collect all study data on such infants as this is a very
interesting
> and
> > problematic group. This would be a great secondary study. Ken, can
> you get
> > this information to us regarding the numbers of infants < 500gm in
> each
> > gestational week. Many thanks All the best over the Holidays and
New
> Year.
> > Neil
> > ----- Original Message -----
> > From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> > To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
> <nfiner@ucsd.edu>;
> > <poo@rti.org>; <adas@rti.org>
> > Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> > <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
> <Wcarlo@peds.uab.edu>;
> > <aaf2@po.cwru.edu>
> > Sent: Friday, December 19, 2003 7:52 AM
> > Subject: RE: protocol
> >
> >
> > > HI,
> > > How about if RTI can give us the number of babies < 500 grams
from
> the
> > > previous analysis of number of babies by gestational age (24,
25,
> 26,
> > > 27)? How does "intent to treat" affect this study, i.e. a 24
week
> 499
> > > gram baby is born - is this child weighed prior to resuscitation
> at
> > > all centers or would we go with the "intent to treat"
> consideration?
> > > Maybe we should say estimated fetal weight of 500 grams or
greater

> for
> > > randomization prior to birth. This would be the "real life"
> scenario.
> > > There may be some < 500 gram infants that find their way into
the
> > > study. Any thoughts from the statisticians also?
> > >
> > > Thanks for the thoughts.
> > > Rose
> > >
> > > -----Original Message-----
> > > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > > Sent: Friday, December 19, 2003 10:42 AM
> > > To: nfiner@ucsd.edu
> > > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins,
> Rosemary
> > > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu;
> aaf2@po.cwru.edu
> > > Subject: protocol
> > >
> > >
> > > Neil,
> > > Sorry that I took so long to get back to you. I think that the
> > > protocol is looking great! I found a couple of typos that I
fixed
> > > with the Word "tracking changes" tool (attached). Have you
> estimated
> > > how many 24 and 25 weekers will be excluded given the 500 gram
> cutoff?
> > > Eventually we will want to describe the sealed envelop
> randomization
> > > method in more detail. How is stratification handled? What
> happens
> > > when the infant is <500g? How do we guarantee sequential
opening
> of
> > > envelops? How do we guarentee that only one envelop is opened
per
> > > infant? Documenting date/time that envelop is opened? Etc.
> > > I wonder if adjusting the pCO2 cutoff for venous gases is a
> necessary
> > > extra bit of complexity?
> > > For treatment arm, 26-27 weeks, I thought the intubation
criteria
> used
> > > to be "may" rather than "must". In our place at present, we
would
> > > certainly not intubate a baby with minimal resp. effort, sat 94,
> good
> > > gases and fiO2 0.55., but we will comply with the protocol. I
> think
> > > this will really increase the number of treatment infants
intubated
> in
> > > this strata. The goal for this group according to the protocol
is
> to
> > > "minimize the duration of intubation of Treatment infants".
> Increasing
> > > the fiO2 req. with the "must" statement would further "separate"

> the
> > > groups which external reviewers apparently wanted.
> > > The protocol would certainly be simpler if it were a comparison
of
> > > early management only, ie CPAP v proph. surf. But, I think want
> we
> > > wanted to test is a management strategy over the first weeks of
> life.
> > > "Separation" is an important issue, so I agree with the strategy
to
> move
> > > to "must" statements.
> > > 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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD); "Edward Donovan"; sduara@miami.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: Fw:COT protocol
Date: Monday, December 22, 2003 4:55:47 PM

It may be preferable to include all 24 weekers and above if full recussitation is planned and exclude the <500 gram infants upon weighing them in the nursery.

Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, December 22, 2003 3:12 PM
To: 'Edward Donovan'; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: Fw:COT protocol

I believe that Ed is right, we should lean towards including them. If we try to exclude them, we may end up losing infants that are in fact > 500 grams BW, but have an estimated fetal weight of < 500 grams. Rose

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Monday, December 22, 2003 4:06 PM
To: Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: Re: Fw:COT protocol

We don't have the denominators, but my impression is that these infants represent only 2-5% of the population at 24 and 25 weeks and less at 26 and 27 weeks. This is small enough to ignore, but we would have a population based study if they are included. They will be randomly distributed between treatment arms. I don't have a strong preference but I lean toward including them.

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> 12/22/2003 10:55:43 AM >>>
Good Morning
Please review this. There appears to be 36 infants of 24-27 weeks who were less than 500 gm in the past year. This is a minimal estimate as the study will be based on best obstetrical estimate and some 23 weekers may be estimated at 24. Overall, I think that the exclusion of such infants is no problem. On the other hand perhaps they ought to be left in for ease of simplicity. We will not know the weights till NICU admission, and thus would have consented and done the DR maneuver. Please let me know your thoughts.
Happy Holidays Neil

----- Original Message -----
From: "Das, Abhik" <adas@rti.org>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Cc: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>; "Poole, W. Kenneth" <poo@rti.org>
Sent: Monday, December 22, 2003 6:26 AM
Subject: RE: protocol

> Please see attached.
> Thanks.
>
> Abhik
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Friday, December 19, 2003 1:28 PM
> To: Higgins, Rosemary (NIH/NICHD); 'Edward Donovan'; poo@rti.org;
> adas@rti.org
> Cc: Kurt Schibler; Vivek Narendran; sduara@miami.edu;
Wcarlo@peds.uab.edu;
> aaf2@po.cwru.edu
> Subject: Re: protocol
>
>
> Hello Everyone
> My thoughts would be that we enroll in the DR, and then remove
following
> weighing in the NICU. This shouldn't effect their care, and should
not
> create an imbalance. I would ask RTI to give us the actual number of
infants
> in these week gestational age groups who weigh less than 500 gm. We
would
> complete a DR form for all such infants, and that would allow us to
track
> such infants using their GDB data. One thought would be to continue
to
> collect all study data on such infants as this is a very interesting
and
> problematic group. This would be a great secondary study. Ken, can
you get
> this information to us regarding the numbers of infants < 500gm in
each
> gestational week. Many thanks All the best over the Holidays and New
Year.
> Neil
> ----- Original Message -----
> From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
> To: "'Edward Donovan'" <Edward.Donovan@cchmc.org>;
<nfiner@ucsd.edu>;
> <poo@rti.org>; <adas@rti.org>
> Cc: "Kurt Schibler" <Kurt.Schibler@cchmc.org>; "Vivek Narendran"
> <Vivek.Narendran@cchmc.org>; <sduara@miami.edu>;
<Wcarlo@peds.uab.edu>;
> <aaf2@po.cwru.edu>
> Sent: Friday, December 19, 2003 7:52 AM
> Subject: RE: protocol
>
>

> > HI,
> > How about if RTI can give us the number of babies < 500 grams from the
> > previous analysis of number of babies by gestational age (24, 25, 26,
> > 27)? How does "intent to treat" affect this study, i.e. a 24 week 499
> > gram baby is born - is this child weighed prior to resuscitation at
> > all centers or would we go with the "intent to treat" consideration?
> > Maybe we should say estimated fetal weight of 500 grams or greater for
> > randomization prior to birth. This would be the "real life" scenario.
> > There may be some < 500 gram infants that find their way into the
> > study. Any thoughts from the statisticians also?
> >
> > Thanks for the thoughts.
> > Rose
> >
> > -----Original Message-----
> > From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
> > Sent: Friday, December 19, 2003 10:42 AM
> > To: nfiner@ucsd.edu
> > Cc: Edward Donovan; Kurt Schibler; Vivek Narendran; Higgins, Rosemary
> > (NIH/NICHD); sduara@miami.edu; Wcarlo@peds.uab.edu; aaf2@po.cwru.edu
> > Subject: protocol
> >
> >
> > Neil,
> > Sorry that I took so long to get back to you. I think that the
> > protocol is looking great! I found a couple of typos that I fixed
> > with the Word "tracking changes" tool (attached). Have you estimated
> > how many 24 and 25 weekers will be excluded given the 500 gram cutoff?
> > Eventually we will want to describe the sealed envelop randomization
> > method in more detail. How is stratification handled? What happens
> > when the infant is <500g? How do we guarantee sequential opening of
> > envelops? How do we guarentee that only one envelop is opened per
> > infant? Documenting date/time that envelop is opened? Etc. I wonder
> > if adjusting the pCO2 cutoff for venous gases is a necessary
> > extra bit of complexity?
> > For treatment arm, 26-27 weeks, I thought the intubation criteria used
> > to be "may" rather than "must". In our place at present, we would
> > certainly not intubate a baby with minimal resp. effort, sat 94, good
> > gases and fiO2 0.55., but we will comply with the protocol. I think
> > this will really increase the number of treatment infants intubated in
> > this strata. The goal for this group according to the protocol is

to
> > "minimize the duration of intubation of Treatment infants".
Increasing
> > the fiO2 req. with the "must" statement would further "separate"
the
> > groups which external reviewers apparently wanted.
> > The protocol would certainly be simpler if it were a comparison of
> > early management only, ie CPAP v proph. surf. But, I think want
we
> > wanted to test is a management strategy over the first weeks of
life.
> > "Separation" is an important issue, so I agree with the strategy to
move
> > to "must" statements.
> > 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
>
>

Percentage of GDB (born between October 2002 to September 2003) infants with gestational age between 24-27 weeks and Birth weight less than 500 grams.

The FREQ Procedure

Gestational Age (weeks)

gage	Frequency	Percent	Cumulative Frequency	Cumulative Percent
< 24	70	63.64	70	63.64
24-27	36	32.73	106	96.36
> 27	4	3.64	110	100.00

Gestational Age (weeks)

OBGGAWKS	Frequency	Percent	Cumulative Frequency	Cumulative Percent
24	13	36.11	13	36.11
25	11	30.56	24	66.67
26	8	22.22	32	88.89
27	4	11.11	36	100.00

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: DR CPAP
Date: Tuesday, December 16, 2003 9:54:52 AM

Ok, I will start working on this.

And yes, today is better. Thanks for asking.
Talk to you soon!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, December 16, 2003 9:52 AM
To: 'petrie@rti.org'
Subject: DR CPAP

Carolyn
(b) (6) [redacted]. The DR CPAP enrollment will be 1345 infants. It will probably take 2+ years - lets do the budget over a three year cycle.

Thanks
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Prenatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT Trial
Date: Wednesday, December 10, 2003 8:39:35 PM

Thanks Rose

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: 'Neil Finer'
Sent: Wednesday, December 10, 2003 10:13 AM
Subject: RE: COT Trial

Neil
Hot Topics was good. There was a significant discussion on where sats should be kept and it was clearly identified that a trial is necessary. No real CPAP discussions though. I'll look at the protocol and hopefully we can get a version soon for the PI's.
Thanks for the hard work
Rose

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, December 09, 2003 5:35 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Cc: Chris Henderson; wrich@ucsd.edu
Subject: COT Trial

Hello Everyone
How was Hot Topics? Here is new version of the COT protocol. Please see my additions, changes and questions in yellow and green. I have added some new references.
In my view this is clean, workable and Alan and Rose agreed that simpler was better. If centers are not willing to change practice, then they should opt out. I want to keep the Treatment and Control Groups different. Also please get back to me regarding the Pulse oximeter table of altered values. Masimo is waiting.
Regards
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

Dec 5, 2003

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 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 ≥ 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 (≤ 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. Infants < 500 gm will not be enrolled due to their high mortality, 83% - 84% from Network review, and the difficulty in early extubation of such infants. 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. Are we doing the same intervention in both strata and can we ask the question of BPD ROP etc. The smaller strata are getting surf vs the larger ones, and after 1 hr the get extubated. I have gone back to our original design.

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 who have a birth weight of 500 gm or greater
- 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
- Infants with a birth weight < 500 gm

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 my 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 ±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 ≥ 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?? (Your thoughts)
- 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, PvCO2 < 70 torr)
- 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 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.

For the Vent Group Only!!
I have simplified this protocol to the following:
CPAP vs Prophylactic surf for all – In reviewing the comments and our protocol, it became clear that we had 2 studies -1) Early vs Later extubation for the 24-25 wks 2) CPAP vs Proph Surf for the 25-26 weekers.
That doesn't work using a single hypothesis and sample size for all. We originally wanted CPAP vs Prop Surf and the reviewers have indicated that that would be clearer and of course Columbia indicates that Surf isn't needed for all 24-25 wks.
I have removed the optional clauses like MAY, and changed the extubation criteria to 15 bpm. In addition the windows for the criteria are now 14 and 7 days reflecting the actual duration of ventilations. Should the window be kept longer for the 24 – 25 wks? They stay intubated about 20 days or longer???

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 (Should this be 72 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
- $PaCO_2$ < 55 torr and pH > 7.25(arterial or capillary samples, if venous PvCO2 < 60 torr)
- 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.

Note that we use the wording of ***MAY*** has been removed and replaced with ***MUST*** in response to the External critiques that the groups would not be well separated be attempted.

Clinicians who would wish to continue ventilation for such infants may do so, as a protocol violation. There are currently no standard criteria for extubation of such infants. 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. These criteria are mild and I feel that these may be a problem. If we change they will be closer to the Treatment group. If the study is about prophylactic surfactant vs CPAP will subsequent criteria for re-intubation be an issue. I would appreciate your thoughts.

- $PaCO_2$ > 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 <u>MUST</u> be intubated if they meet <u>ANY</u> 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 (Note that the average PaCO2 prior to intubation in the DR

Feasibility trial was 54 ± 9.9 torr and the pH was 7.3 ± 0.1 (arterial or capillary samples, if venous subtract 5 torr from PCO2) I would prefer that this section is not included and that it is a violation not to provide prophylactic surf to all Control infants. This is clean, follows current evidence, and should not increase surfactant use as the Treatment infants will not be receiving and thus overall I would anticipate that surfactant use would decrease in this stratum

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

- $PaCO_2$ < 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) with a pH > 7.25
- 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.

Note that we had used the wording of ***MAY*** be attempted. We have changed this to must to ensure closer adherence to this protocol. WE are not specifying a weaning protocol, so that we are leaving significant room for the individual clinicians to get to these settings. I would hope that we could avoid developing stringent criteria.

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.

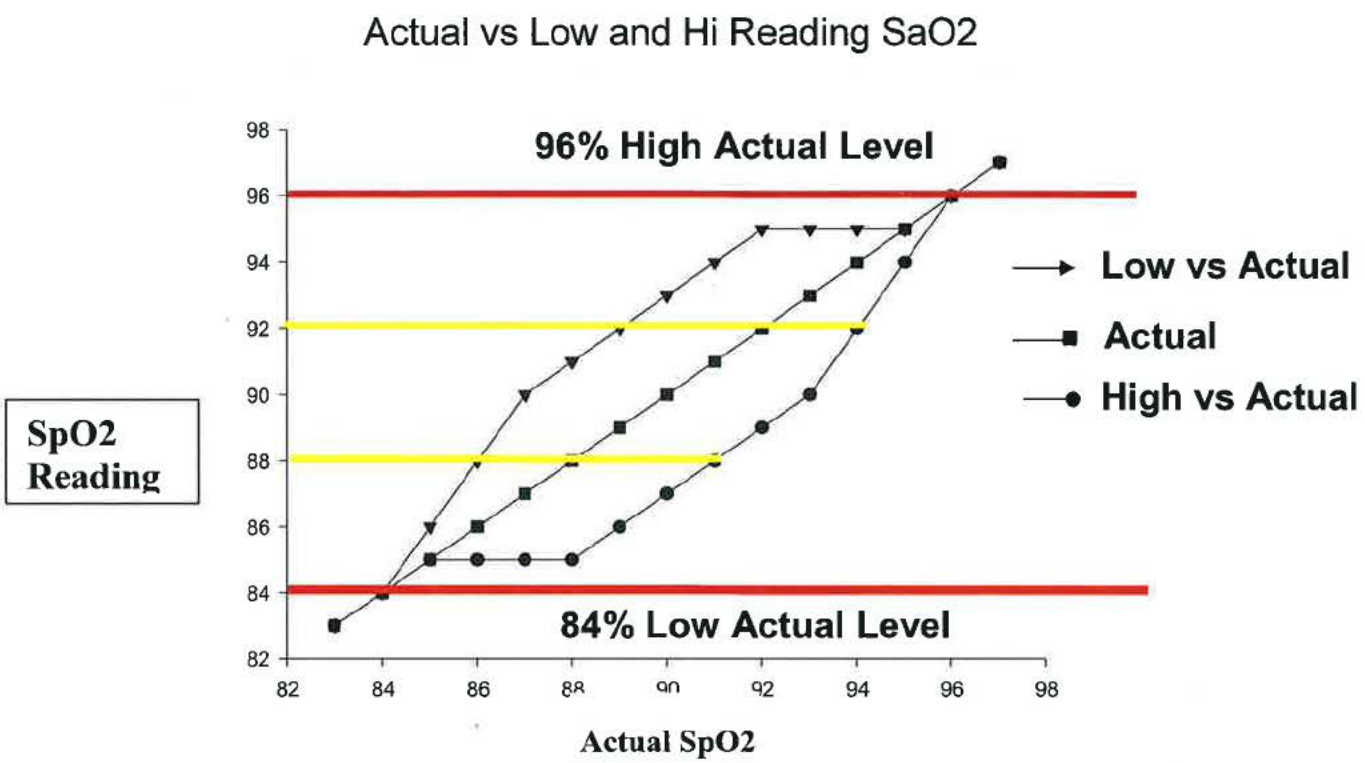
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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 ≥ 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:	Mike Petterson
Cc:	wrich@ucsd.edu; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: Please reviews these tables for Displaying SpO2
Date:	Wednesday, December 10, 2003 11:10:00 AM
Attachments:	Tables with hi and lo- modified.doc

Mike
In looking at these tables I have the following comments:
The Low range ie 85-89 = 88-92. The PO should have actual = reading at 96% for both ranges. I would change the readings as indicated in the revised Table in yellow
The High range looks good.
I will await further comments from my colleagues and will try to speak to Cynthia today.
Regards
Neil----- Original Message -----
From: "Mike Petterson" <MPetters@masimo.com>
To: "'Neil Finer'" <nfiner@ucsd.edu>; "'Wade Rich'" <wrich@ucsd.edu>
Sent: Wednesday, December 03, 2003 3:17 PM
Subject: Please reviews these tables for Displaying SpO2

> Gentlemen,
>
> Please take a look at these tables. Ammar needs unique numbers to be able to
> display "modified" numbers then be able to dump the real data later.
>
> Ammar believes he can show the "modified" numbers in trend the way you
> requested - thus the clinicians can see how well they are keeping the
> infants in the 88 to 93% range. However, this "modified" data will be
> downloaded as the true unmodified SpO2.
>
> Please let us know if this is acceptable ASAP. By the way, my new cell phone
> number is 949-697-4302.
>
> Best regards,
>
> Mike
> <<Tables with hi and lo.doc>>
>
>
>
> **********
>
> CONFIDENTIALITY NOTICE
> This e-mail communication may contain information that is proprietary,
> confidential and/or privileged from disclosure under applicable law. If the
> reader of this e-mail is not the intended recipient, you are hereby notified
> that use, copying, dissemination or continued possession of this
> communication is strictly prohibited. If you have any reason to believe you
> are not the intended recipient of this e-mail, please notify us immediately

> by e-mail to postmaster@masimo.com, delete all copies of this e-mail from
> computer memory or storage and return all hard-copies via regular mail to
> Masimo, 2852 Kelvin Avenue, Irvine, California, U.S.A. 92614. Thank you.
>
>

Low reading	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Actual SpO_2	83	84	84.6	84.8	85.1	85.3	86.3	87.2	88.2	89.1	91	92.5	94	96	97	98	99	100

High reading	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Actual SpO_2	83	84	86.5	89	89.9	90.9	91.8	92.7	93.6	94.6	95.5	95.7	95.8	96	97	98	99	100

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Fw: 24-25 week days ventilated
Date: Saturday, December 06, 2003 1:48:41 PM

---

yes. I think it would help.
How many survivors are never ventilated and how many receive ventilation only after 2-3 days.

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> 12/06/2003 11:58:03 AM >>>

Ed
Ken may be able to get this info also - It may be worth getting to critically evaluate - let me know if you think it will help and I'll send
Ken a list of items for the 24-25 week babies.
Thanks for the comments!
Rose
-----Original Message-----
From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Sent: 12/6/2003 11:14 AM
Subject: Re: Fw: 24-25 week days ventilated

Neil,
I don't think this would be a problem, but the data don't tell the whole story - at least in Cincinnati. It does not reflect those who do not receive ventilator and survive and it doesn't account for those who do well on CPAP for a week or so and then receive a little or a lot of MV.

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> 12/05/03 13:47 PM >>>
Hello all,
I had these numbers pulled in preparation for revising the protocol. I would like to suggest that the control arm infants of 24 and 25 weeks

cannot be extubated for a minimum of 48 hours. Do you think this is reasonable? Certainly, the Network numbers would support this approach.
Regards,
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Alan Jobe (E-mail) ; Neil Finer (E-mail)
Sent: Thursday, December 04, 2003 11:31 AM
Subject: 24-25 week days ventilated

Neil and Alan
the numbers for days on the vent are higher than predicted!!
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: "Neil Finer"; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: 24-25 week days ventilated
Date: Friday, December 05, 2003 10:53:35 PM

THe data that would be most useful is the % of infants per center who spent less than 48 hours on the vent and were alive by this time. Mean data can be deceiving for the question of interest. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, December 05, 2003 12:51 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Fw: 24-25 week days ventilated

Hello all,
I had these numbers pulled in preparation for revising the protocol. I would like to suggest that the control arm infants of 24 and 25 weeks cannot be extubated for a minimum of 48 hours. Do you think this is reasonable? Certainly, the Network numbers would support this approach.
Regards,
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Alan Jobe (E-mail) ; Neil Finer (E-mail)
Sent: Thursday, December 04, 2003 11:31 AM
Subject: 24-25 week days ventilated

Neil and Alan
the numbers for days on the vent are higher than predicted!!
Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff"; Neil Finer; Shahnaz Duara; Neil Finer; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Fw: 24-25 week days ventilated
Date: Friday, December 05, 2003 10:44:17 PM

I think this is reasonable. I would prefer to focus the intervention on the intervention group and not in the control group but this practice may be somewhat uniform already in the Network now. Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 05, 2003 3:45 PM
To: 'Avroy A. Fanaroff'; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Fw: 24-25 week days ventilated

It looks like people have practiced "longer intubation" when one looks at the data.

Rose

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Friday, December 05, 2003 4:35 PM
To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: Fw: 24-25 week days ventilated

Hi
Sounds OK to me - I can live with it - interesting numbers
Yogi berra was right after all - you can see a lot by observing.
Av
At 01:51 PM 12/5/2003, Neil Finer wrote:

Hello all,
I had these numbers pulled in preparation for revising the protocol. I would like to suggest that the control arm infants of 24 and 25 weeks cannot be extubated for a minimum of 48 hours. Do you think this is reasonable? Certainly, the Network numbers would support this approach.
Regards,
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Alan Jobe (E-mail) ; Neil Finer (E-mail)
Sent: Thursday, December 04, 2003 11:31 AM
Subject: 24-25 week days ventilated

Neil and Alan
the numbers for days on the vent are higher than predicted!!
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)

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu is changing to

avroy.fanaroff@case.edu

Phone 216-844-3884
Fax 216-844-1479

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: Please reviews these tables for Displaying SpO2
Date: Friday, December 05, 2003 1:34:16 PM

Would you all please review this table and let me know if you think that this scheme is appropriate.

Regards,
Neil

----- Original Message -----
From: "Mike Petterson" <MPetters@masimo.com>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Sent: Friday, December 05, 2003 8:48 AM
Subject: RE: Please reviews these tables for Displaying SpO2

> Are you at Hot Topics also??
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Friday, December 05, 2003 8:47 AM
> To: Mike Petterson
> Subject: Re: Please reviews these tables for Displaying SpO2
>
>
> Thanks Mike
> I am asking the core study group to review this and they are all at Hot
> Topics. I will get back to you by Wednesday.
> Neil Finer
> ----- Original Message -----
> From: "Mike Petterson" <MPetters@masimo.com>
> To: "'Neil Finer'" <nfiner@ucsd.edu>; "'Wade Rich'" <wrich@ucsd.edu>
> Sent: Wednesday, December 03, 2003 3:17 PM
> Subject: Please reviews these tables for Displaying SpO2
>
>
> > Gentlemen,
> >
> > Please take a look at these tables. Ammar needs unique numbers to be
able
> to
> > display "modified" numbers then be able to dump the real data later.
> >
> > Ammar believes he can show the "modified" numbers in trend the way you
> > requested - thus the clinicians can see how well they are keeping the
> > infants in the 88 to 93% range. However, this "modified" data will be
> > downloaded as the true unmodified SpO2.
> >
> > Please let us know if this is acceptable ASAP. By the way, my new cell
> phone
> > number is 949-697-4302.
> >
> > Best regards,
> >

> > Mike
> > <<Tables with hi and lo.doc>>
> >
> >
> >
> > **********
> >
> > CONFIDENTIALITY NOTICE
> > This e-mail communication may contain information that is proprietary,
> > confidential and/or privileged from disclosure under applicable law. If
> the
> > reader of this e-mail is not the intended recipient, you are hereby
> notified
> > that use, copying, dissemination or continued possession of this
> > communication is strictly prohibited. If you have any reason to believe
> you
> > are not the intended recipient of this e-mail, please notify us
> immediately
> > by e-mail to postmaster@masimo.com, delete all copies of this e-mail
from
> > computer memory or storage and return all hard-copies via regular mail
to
> > Masimo, 2852 Kelvin Avenue, Irvine, California, U.S.A. 92614. Thank
you.
> >
> >
>

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD); M. D. Alan Jobe (Jobea0@chmcc.org); M. D. Neil Finer (nfiner@ucsd.edu)
Cc: Petrie, Carolyn; Heidi Squibb (UCSD) (hsquibb@ucsd.edu)
Subject: COT Conf. Call Today 1pm EST (10PST)
Date: Wednesday, December 03, 2003 9:35:27 AM

Dear All-

The conference call to discuss the COT trial and reviews, is scheduled for **Today** (Wed, Dec 3) at **1pm EST (10am PST).**

To Join the Call
Dial toll free: **866-675-**(b) (6)
Passcode: (b) (6)

Leader: Rose Higgins

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: reviews
Date: Tuesday, December 02, 2003 7:56:51 PM

Many thanks Rose
I will be here tomorrow and Thursday till about 11:00 AM my time.
Neil
----- Original Message -----
From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>
To: "'Neil Finer '" <nfiner@ucsd.edu>
Sent: Tuesday, December 02, 2003 3:54 PM
Subject: RE: reviews

> Neil
> I think that some of the COlumbia suggestions are not feasible. How about
I
> set up a call with you, ALan and I and we can discuss changes, if any??
> Let me know
> Rose
>
> -----Original Message-----
> From: Neil Finer
> To: Higgins, Rosemary (NIH/NICHD)
> Sent: 12/2/2003 6:44 PM
> Subject: Re: reviews
>
> Hello Rose
> I would like to ask for some direction. Are we to redesign this trial to
> satisfy the outside reviewers? Will any revision go back to these
> reviewers for approval? Is this the process used for all Network trials?
> Was it used for the Candida trial?
> At this rate, I will spend all of my time trying to satisfy someone's
> concerns. While many points are relevant, the protocol looks like it
> does because we tried to appease many centers who did not want
> surfactant for all control infants of 26-27 weeks, who did not want a
> simple resp rate cutoff for extubation, who wanted exclusion criteria
> for poor perfusion PDA etc. None of these were in our initial protocol.
> The critique from Columbia is the very reason this trial needs doing, we
> cannot assume that their practices are the model to be followed.
> As we had stated earlier, there appears little enthusiasm for this trial
> which has been modified to satisfy a number of centers, and we now have
> to defend many of those modifications.
> I am leery of redesigning this trial to its original and cleaner form,
> as I suspect the steering committee will have even less enthusiasm than
> before.
> I will try to call you to discuss these issues in more depth.
> Regards
> Neil Finer
>
>
> ----- Original Message -----
> From: Higgins, <mailto:higginsr@mail.nih.gov> Rosemary (NIH/NICHD)
> To: Neil Finer (E-mail) <mailto:nfiner@ucsd.edu>
> Cc: Alan Jobe (E-mail) <mailto:jobea0@chmcc.org>
> Sent: Tuesday, November 25, 2003 12:18 PM
> Subject: reviews

>
> Neil
> Attached are the outside reviews that I have received for the COT trial.
> There are concerns with the CPAP portion of the trial and
> intubation/extubation criteria. Please address the concerns and bring
> them back to the Steering committee for comment. If you would like us
> to facilitate distribution of the comments to the subcommittee members,
> let me know. I wanted you to have a chance to review the critiques
> first.
> Thanks and I look forward to hearing from you.
>
> 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: CHMCC Groupwise
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT
Date: Monday, December 01, 2003 9:56:33 AM

The reviews are a bit all over the place - Polin's suggestions are just not doable. - and of course conflict with others. Happy to talk with you or Neil about how to proceed. Hope you had a good weekend.

Alan H. Jobe, MD, PhD
Professor of Pediatrics
Division of Pulmonary Biology/Neonatology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue, ML#7029
Cincinnati, Ohio 45229
ph: 513-636-8563
fax: 513-636-8691
E-mail: alan.jobe@cchmc.org

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Cc: Petrie, Carolyn
Subject: COT Review
Date: Monday, November 24, 2003 12:57:38 PM
Attachments: COT Reviews 11_24_03.doc

Carolyn Petrie

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

Reviewer #1

interesting - I'm still reflecting - but it seems to me you will need to address PCO2 levels - both background/previous studies - and more guidelines to use during study to be sure that outcome isn't affected by different approaches - i believe a few other things also will need some agreement: - PDA management/???Nitric Oxide??/feeding approaches/Vit A etc. When we approached using more NCPAP in Philadelphia - we found we needed to reach consensus on managing CO2 first.

Reviewer #2

I'm not sure there's that much I can say about this protocol because it's been 20+ years since I've spent any significant time in the NICU. Consider my comments in that light.

The basic idea is important-- ever since the publication of cross-NICU comparisons in the 1980s there's been a nagging suspicion that very aggressive ventilation strategies, although intuitively beneficial, might not help survival, but rather just increase morbidity, and maybe even harm survival. This study is an attempt to evaluate this in a randomized way. The concept is therefore important.

As a general comment (and my time out of the NICU may not invalidate this), I'm struck by the complexity of the protocol. I just don't have enough recent real-world NICU experience to say how well even a conscientious NICU would be able to follow this protocol. At the least, it would probably be helpful to draw up pictorial flow sheets, laminate them and hang them from the warmer of every baby enrolled in this study. That would provide a handy, immediately available reference to help people stay with the protocol. It would probably also be a good idea to guess at the likely amount of protocol violations there will be and inflate the sample size to account for it.

The following 3 comments may just reflect my lack of recent NICU experience, but I'll provide them anyway.

Page 13 and elsewhere-- might an unanticipated side effect of a "MUST EXTUBATE" limit be that neonatologists will just be slower to wean babies down to that level??? This would be a way for someone who is skeptical of a conservative strategy to thwart the protocol

Same paragraph -- Again, it's been a long time for me, but a rate of 15-20 bpm seems a bit high to go straight to extubation from. I might just be out of date, however.

Page 16-- MUST INTUBATE criteria-- again, I don't know what people are doing in the NICU these days but at least from my recollection, people wouldn't rush to intubate if the FiO2 was only 0.3 and the child seemed to be breathing ok--especially if it's intubation for ventilation as opposed to surfactant administration. At least as I remember they'd let the o2 go a bit higher before intubating. If most NICUs now are not that aggressive (say, they waited until 35 or 40% oxygen was needed before intubating), then the control group would not be a fair representation of what people are doing in practice.

From: Wally Carlo, M.D.
To: "Edward Donovan "; Higgins, Rosemary (NIH/NICHD); "nfiner@ucsd.edu "
Cc: "sduara@miami.edu "; "aaf2@po.cwru.edu "
Subject: RE: Fw: Updated COT Trial
Date: Sunday, November 16, 2003 6:51:50 PM

Sorry for my delayed, but I fully agree we can not continue to change the protocol a bit at a time. Wally

-----Original Message-----
From: Edward Donovan
To: higginsr@mail.nih.gov; Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: sduara@miami.edu; aaf2@po.cwru.edu
Sent: 11/10/2003 12:11 PM
Subject: Re: Fw: Updated COT Trial

no. don't keep modifying protocol for a single center

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

>>> "Neil Finer" <nfiner@ucsd.edu> 11/09/2003 6:50:45 PM >>>
Hi Everyone
In the 26-27 week group we allow infants who require less than 30% oxygen to
not be intubated. Are you suggesting that as Abbot requested, that an infant
intubated in the DR, who then does not require > 30% at 1 hour would not
receive DR surfactant. Remember we initially wanted prophylactic surfactant
in the control group. We then compromised for Abbot and introduced the 30%
criteria. Now we will not intubate Control infants who require intubation in
the DR? All this for one center??
How many such infants do you think meet these criteria? Abbot's unit has the
lowest surfactant use, and he does not want to increase it. Remember that
the Treated infants will have markedly reduced surfactant administration,
and thus I expect a lower use overall at most centers.
Are we going to modify the protocol repeatedly for a single center?
I say enough already.
Your call.
Neil
----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
To: "'Higgins, Rosemary (NIH/NICHD)'" <higginsr@mail.nih.gov>; "'Abbot Laptook'" <Abbot.Laptook@UTSouthwestern.edu>; <nfiner@ucsd.edu>

Cc: <Edward.Donovan@chmcc.org>; <sduara@miami.edu>;
<aaf2@po.cwru.edu>;
"Walid Salhab" <Walid.Salhab@UTSouthwestern.edu>
Sent: Saturday, November 08, 2003 12:11 AM
Subject: RE: Fw: Updated COT Trial

> Sounds good to me. wally
>
> -----Original Message-----
> From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> Sent: Monday, November 03, 2003 6:52 AM
> To: 'Abbot Laptook'; nfiner@ucsd.edu
> Cc: Edward.Donovan@chmcc.org; sduara@miami.edu; Wally Carlo, M.D.;
> aaf2@po.cwru.edu; Walid Salhab
> Subject: RE: Fw: Updated COT Trial
>
>
> Hi
> How about a minimum oxygen requirement (that may be suggestive of
lung
> disease) along with intubation be incorporated to address this
concern??
The
> Survanta patient package insert uses 30% oxygen requirement.
> Thanks
> Rose
>
> -----Original Message-----
> From: Abbot Laptook [mailto:Abbot.Laptook@UTSouthwestern.edu]
> Sent: Saturday, November 01, 2003 1:45 PM
> To: nfiner@ucsd.edu
> Cc: Edward.Donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD);
> sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; Walid
Salhab
> Subject: Re: Fw: Updated COT Trial
>
>
> Neil,
> Sorry I could not get back to you sooner but I have been out of
town.
With
> regards to your question below of a mandatory use of surfactant for
infants
> intubated within 48hr of age (26-27 week strata), we would answer
that
this
> would not be ok with our site. This type of approach does not allow
any
> leeway for infants that are intubated in the delivery room for poor
> respiratory effort, do not have lung disease and are weaning and get
to
room
> air by an hour of age (we do not give these infants surfactant).
The
> protocol as it stands now does not address this issue. For the
latter
> infants that are extubated on day 1 but develop atelectasis, oxygen
> requirement and are put back on the ventilator at less than 48hr of
age,

we
> do not give surfactant. We do give surfactant up to 48 hrs of age
but
this
> is uncommon. Most is given on day 1 and occassionaly up to 36 hours.
Abbot
> >>> "Neil Finer" <nfiner@ucsd.edu> 10/27/03 12:47:33 PM >>>
> Abbot
> I tried to call you today, but I missed you. Surfactant will be an
issue
> only for the 26-27 week treated infants. Would you be OK with a
mandatory
> use of surfactant if these infants require intubation within 48 hrs
of
> birth, and that after that, it is left to the site? This was not
intended
to
> be a study of surfactant in these infants, but rather a safeguard for
the
> treatment infants who need intubation. Neil
> ----- Original Message -----
> From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> To: <nfiner@ucsd.edu>
> Cc: <HigginsR@mail.nih.gov>; "Walid Salhab"
> <Walid.Salhab@UTSouthwestern.edu>
> Sent: Sunday, October 26, 2003 11:07 AM
> Subject: Re: Fw: Updated COT Trial
>
>
> > Neil,
> > These responses are very helpful. With regards to the pH, we
> > presently do not have a firm pH or pCO2 for reintubation when we
are
> > dealing with established or clearly evolving BPD. Specifically if
we
> had
> > an infant off the ventilator at more than 2 weeks of age, most of
us
> >would try to maintain the infant off the ventilator if the pCO2 was
55
> > but the pH maintained >7.20-7.25 even with an FiO2 > 50%. I think
we
> do
> > realize that we have moved to this strategy without data but what
> drives
> > it is reducing the time on mechanical ventilation. I think your
> > suggestion of using the intubation criteria of the protocol for
the
> > first 14 days is very reasonable from our perspective. With regard
> to
> > point 3 and surfactant, what we are concerned with is the initail
> dose
> > of surfactant. We do not use surfactant past 48 hours and rarely
use
> it
> > after 36 hours. I am not sure if I am misinterpreting the protocol
> but
> > if an infant ends up on CPAP and 35% O2 at 60 hours of age with
> apnea
> > and atelectasis but never had surfactant previously, they would

now
> need
> > to get surfactant. Now that you raise the repeat dosing of
> surfactant
> > above, that should be clarified.
> > I appreciate your response Neil. Abbot
> >
> > >>> "Neil Finer" <nfiner@ucsd.edu> 10/26/03 12:38:39 PM >>>
> >
> > > Hello Abbot
> > > I will try to answer all your questions.
> > > 1) Staging in the 2 Strata. This may be an option, and it may
> help
> > some
> > > sites. We would prefer to start both strata together. The
criteria
> > for
> > > intubation and extubation are similar between these strata and
> > actually as
> > > the smaller infants all get prophylactic surfactant, this may be
> > easier to
> > > manage. I will ask RTI if initiated the study at some sites for
> only
> > 1
> > > strata represents a problem. Our Subcommittee is OK with this
> > modification.
> > > 2) We removed pH thinking that the sites were sending the
message
> > that we
> > > were too prescriptive. Reintubation is only mandated for the
> Control
> > > Infants, and we can certainly add the pH if you think that this
is
> > helpful.
> > > Will your group currently not re-intubate a baby with a PaCO2 >
55
> > and an
> > > Oxygen requirement > 50% if the pH is > 7.25 but would if the pH
> was
> > <
> > 7.25?
> > > What pH are you currently using? Would they accept these
criteria
> for
> > the
> > > first 7-14 days?
> > > We could take the position that after the first 7 days
> re-intubation
> > will
> > be
> > > a local decision, and let the protocol separate the infants out
by
> > initial
> > > management.
> > > 3) The protocol says that repeat surfactant may be given and
does
> > not
> > force
> > > the use of additional doses in either strata. We will ensure
that

> > this
> > > message is clearly stated in the final protocol and study
manual.
> > > 4) Any form of CPAP may be used. We are hopeful that the bubble
> CPAP
> > may
> > be
> > > available by the time of the study initiation, but is has yet to
> > receive
> > FDA
> > > approval.
> > > I hope that these responses are helpful.
> > > Neil
> > > ----- Original Message -----
> > > From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> > > To: <petrie@rti.org>; <nfiner@ucsd.edu>
> > > Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>;
"Walid
> > Salhab"
> > > <Walid.Salhab@UTSouthwestern.edu>
> > > Sent: Friday, October 17, 2003 5:44 PM
> > > Subject: RE: Updated COT Trial
> > >
> > >
> > > > Carolyn, Neil,
> > > > Here is the feedback from the UT-Southwestern site. Almost
> > everyone
> > > > is on board and if I can get some good feedback on the
following
> > issues
> > > > I think that this site will be in. There are 3 sticking points
> as
> > > > followsn and the fourth point is minor:
> > > >
> > > > 1) Complexity of the intervention: Everyone agrees that this
is
> a
> > very
> > > > complicated study that will be a challenge to do. Most
everyone
> is
> > ready
> > > > to give it a try at this point but a few are very concerned
> about
> > > > feasibilty given that within the ventilation arm of the study,
> > there are
> > > > in essence 4 groups (based on the 2 strata), and each has some
> > specific
> > > > issues. We would like to offer a potential solution which may
> > appease
> > > > many at this and other sites: Consider staging the initiation
of
> > the
> > > > study such that for the first 4-6 months the study only enters
> > infants
> > > > in the 26-27 wk strata and subsequently the 24-25 week strata
is
> > then
> > > > initiated. This will allow people to get accustomed to the
study

> in
> > a
> > > > group which may be more stable and with less problems, and take
> > care of
> > > > unanticipated problems which invariably will come up (as we
> > encountered
> > > > with the SAVE trial). This should help deal with the feasibiltiy
> > issues
> > > > that so many attendings are concerned about since it will be
> easier
> > to
> > > > focus on 2 groups within the ventilation arm rather than 4.
> > > >
> > > > 2) Re-Intubation Criteria: A number of people expressed concern
> > that
> > > > re-intubation criteria should have a pH associated with it if
> > these
> > > > criteria are to be extended over such a long time interval of 28
> > days.
> > > > For example, at 14-28 days if we had an infant with a well
> > compensated
> > > > respiratory acidosis even with a high oxygen requriement, we
> would
> > still
> > > > try to keep the infant off the ventilator. This reflects the
> > movement of
> > > > this site to a more permissive strategy for right or wrong
> reasons.
> > It
> > > > is difficult to get people to move from this management (even
> > though we
> > > > have no data to say it is right) given that the intervention
> will
> > > > prolong time on the ventilator. I thiink I have been successful
> > in
> > > > getting people to understand that it is critical to have
> > separation
> > > > between groups and maybe including a pH will obviate that.
> However,
> > some
> > > > further discussion regarding this issue would benefit our site.
> > > >
> > > > 3) Use of surfactant up to 72 hours: We will not give surfactant
> > after
> > > > 48 hours (we rarely give now after 36 hours) since it does not
> work
> > well
> > > > and we will be wasting the preparation. We are under heavy
> pressure
> > to
> > > > watch our costs and using surfactant at such a late post-natal
> age
> > will

> > > > not sit well with Administration since the study is so
different
> > from
> > > > > our practice. If other centers use it at 36-72 hours of age,
> fine,
> > but
> > > > > build in a window of time for surfactant use so we don't get
> dinged
> > with
> > > > > violations for something we will not do.
> > > > >
> > > > > 4) Type of CPAP: Clarify what type of CPAP will be acceptable
> for
> > the
> > > > > study and what type of equipment we will need.
> > > > >
> > > > > Hope this helps. I think this site is moving in the right
> > direction.
> > > > > Sorry for the late response but by my watch it is still 10/17.
> AL
> > > > >
> > > > > >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> > > > > Reminder that today is the deadline for your comments:
> > > > >
> > > > >
> > > > > To the Neonatal Research Network Steering Committee:
> > > > >
> > > > > Attached is the latest COT trial for your input. Please send
> > comments
> > > > > by
> > > > > Friday, October 17.
> > > > >
> > > > > Thanks!
> > > > >
> > > > > Carolyn
> > > > >
> > > > >
> > > > >
> > > > >
> > > > >
> > > >
> > > >
> > >
> > >

From: Avroy A. Fanaroff
To: Edward Donovan; Higgins, Rosemary (NIH/NICHD); WCarlo@PEDS.UAB.EDU; nfiner@ucsd.edu
Cc: sduara@miami.edu; aaf2@cwru.edu
Subject: Re: Fw: Updated COT Trial
Date: Monday, November 10, 2003 1:38:11 PM

Hi
The time for modifying is over
it is time for action
Them what can't do the study - shouldn't.
it is not an easy study, we have said that many times; we know it is feasible from the pilot trial;it's time to Fish or cut bait. I am ready to fish.
Agree with Ed
Av
At 01:11 PM 11/10/2003, Edward Donovan wrote:
>no. don't keep modifying protocol for a single center
>
>Edward F. Donovan, M.D.
>Director
>Child Policy Research Center
>Children's Hospital Medical Center
>3333 Burnet Avenue, ML 7014
>Cincinnati, OH 45229-3039
>Phone 513-636-0182
>Fax 513-636-0171
>www.cprc-chmc.uc.edu
>
> >>> "Neil Finer" <nfiner@ucsd.edu> 11/09/2003 6:50:45 PM >>>
>Hi Everyone
>In the 26-27 week group we allow infants who require less than 30% >oxygen to
>not be intubated. Are you suggesting that as Abbot requested, that an >infant
>intubated in the DR, who then does not require > 30% at 1 hour would >not
>receive DR surfactant. Remember we initially wanted prophylactic >surfactant
>in the control group. We then compromised for Abbot and introduced the >30%
>criteria. Now we will not intubate Control infants who require >intubation in
>the DR? All this for one center??
>How many such infants do you think meet these criteria? Abbot's unit >has the
>lowest surfactant use, and he does not want to increase it. Remember >that
>the Treated infants will have markedly reduced surfactant >administration,
>and thus I expect a lower use overall at most centers.
>Are we going to modify the protocol repeatedly for a single center?
>I say enough already.
>Your call.
>Neil
>----- Original Message -----
>From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
>To: "'Higgins, Rosemary (NIH/NICHD)'" <higginsr@mail.nih.gov>; "'Abbot >Laptook'" <Abbot.Laptook@UTSouthwestern.edu>; <nfiner@ucsd.edu>

>Cc: <Edward.Donovan@chmcc.org>; <sduara@miami.edu>;
><aaf2@po.cwru.edu>;
>"Walid Salhab" <Walid.Salhab@UTSouthwestern.edu>
>Sent: Saturday, November 08, 2003 12:11 AM
>Subject: RE: Fw: Updated COT Trial
>
>
> > Sounds good to me. wally
> >
> > -----Original Message-----
> > From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
> > Sent: Monday, November 03, 2003 6:52 AM
> > To: 'Abbot Laptook'; nfiner@ucsd.edu
> > Cc: Edward.Donovan@chmcc.org; sduara@miami.edu; Wally Carlo, M.D.;
> > aaf2@po.cwru.edu; Walid Salhab
> > Subject: RE: Fw: Updated COT Trial
> >
> >
> > Hi
> > How about a minimum oxygen requirement (that may be suggestive of
>lung
> > disease) along with intubation be incorporated to address this
>concern??
>The
> > Survanta patient package insert uses 30% oxygen requirement.
> > Thanks
> > Rose
> >
> > -----Original Message-----
> > From: Abbot Laptook [mailto:Abbot.Laptook@UTSouthwestern.edu]
> > Sent: Saturday, November 01, 2003 1:45 PM
> > To: nfiner@ucsd.edu
> > Cc: Edward.Donovan@chmcc.org; Higgins, Rosemary (NIH/NICHD);
> > sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; Walid
>Salhab
> > Subject: Re: Fw: Updated COT Trial
> >
> >
> > Neil,
> > Sorry I could not get back to you sooner but I have been out of
>town.
>With
> > regards to your question below of a mandatory use of surfactant for
>infants
> > intubated within 48hr of age (26-27 week strata), we would answer
>that
>this
> > would not be ok with our site. This type of approach does not allow
>any
> > leeway for infants that are intubated in the delivery room for poor
> > respiratory effort, do not have lung disease and are weaning and get
>to
>room
> > air by an hour of age (we do not give these infants surfactant).
>The
> > protocol as it stands now does not address this issue. For the
>latter
> > infants that are extubated on day 1 but develop atelectasis, oxygen
> > requirement and are put back on the ventilator at less than 48hr of
>age,

>we
> > do not give surfactant. We do give surfactant up to 48 hrs of age
>but
>this
> > is uncommon. Most is given on day 1 and occassionaly up to 36 hours.
>Abbot
> > >>> "Neil Finer" <nfiner@ucsd.edu> 10/27/03 12:47:33 PM >>>
> > Abbot
> > I tried to call you today, but I missed you. Surfactant will be an
>issue
> > only for the 26-27 week treated infants. Would you be OK with a
>mandatory
> > use of surfactant if these infants require intubation within 48 hrs
>of
> > birth, and that after that, it is left to the site? This was not
>intended
>to
> > be a study of surfactant in these infants, but rather a safeguard for
>the
> > treatment infants who need intubation. Neil
> > ----- Original Message -----
> > From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> > To: <nfiner@ucsd.edu>
> > Cc: <HigginsR@mail.nih.gov>; "Walid Salhab"
> > <Walid.Salhab@UTSouthwestern.edu>
> > Sent: Sunday, October 26, 2003 11:07 AM
> > Subject: Re: Fw: Updated COT Trial
> >
> >
> > > Neil,
> > > These responses are very helpful. With regards to the pH, we
> > > presently do not have a firm pH or pCO2 for reintubation when we
>are
> > > dealing with established or clearly evolving BPD. Specifically if
>we
> > had
> > > an infant off the ventilator at more than 2 weeks of age, most of
>us
> > >would try to maintain the infant off the ventilator if the pCO2 was
>55
> > > but the pH maintained >7.20-7.25 even with an FiO2 > 50%. I think
>we
> > do
> > > realize that we have moved to this strategy without data but what
> > drives
> > > it is reducing the time on mechanical ventilation. I think your
> > > suggestion of using the intubation criteria of the protocol for
>the
> > > first 14 days is very reasonable from our perspective. With regard
> > to
> > > point 3 and surfactant, what we are concerned with is the initail
> > dose
> > > of surfactant. We do not use surfactant past 48 hours and rarely
>use
> > it
> > > after 36 hours. I am not sure if I am misinterpreting the protocol
> > but
> > > if an infant ends up on CPAP and 35% O2 at 60 hours of age with
> > apnea
> > > and atelectasis but never had surfactant previously, they would

>now
> > need
> > > to get surfactant. Now that you raise the repeat dosing of
> > surfactant
> > > above, that should be clarified.
> > > I appreciate your response Neil. Abbot
> > >
> > > >>> "Neil Finer" <nfiner@ucsd.edu> 10/26/03 12:38:39 PM >>>
> > >
> > > > Hello Abbot
> > > > I will try to answer all your questions.
> > > > 1) Staging in the 2 Strata. This may be an option, and it may
> > help
> > > some
> > > > sites. We would prefer to start both strata together. The
>criteria
> > > for
> > > > intubation and extubation are similar between these strata and
> > > actually as
> > > > the smaller infants all get prophylactic surfactant, this may be
> > > easier to
> > > > manage. I will ask RTI if initiated the study at some sites for
> > only
> > > 1
> > > > strata represents a problem. Our Subcommittee is OK with this
> > > modification.
> > > > 2) We removed pH thinking that the sites were sending the
>message
> > > that we
> > > > were too prescriptive. Reintubation is only mandated for the
> > Control
> > > > Infants, and we can certainly add the pH if you think that this
>is
> > > helpful.
> > > > Will your group currently not re-intubate a baby with a PaCO2 >
>55
> > > and an
> > > > Oxygen requirement > 50% if the pH is > 7.25 but would if the pH
> > was
> > > <
> > > 7.25?
> > > > What pH are you currently using? Would they accept these
>criteria
> > for
> > > the
> > > > first 7-14 days?
> > > > We could take the position that after the first 7 days
> > re-intubation
> > > will
> > > be
> > > > a local decision, and let the protocol separate the infants out
>by
> > > initial
> > > > management.
> > > > 3) The protocol says that repeat surfactant may be given and
>does
> > > not
> > > force
> > > > the use of additional doses in either strata. We will ensure
>that

> > > this
> > > > message is clearly stated in the final protocol and study
>manual.
> > > > > 4) Any form of CPAP may be used. We are hopeful that the bubble
> > CPAP
> > > may
> > > be
> > > > available by the time of the study initiation, but is has yet to
> > > receive
> > > FDA
> > > > approval.
> > > > I hope that these responses are helpful.
> > > > Neil
> > > > ----- Original Message -----
> > > > From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> > > > To: <petrie@rti.org>; <nfiner@ucsd.edu>
> > > > Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>;
>"Walid
> > > Salhab"
> > > > <Walid.Salhab@UTSouthwestern.edu>
> > > > Sent: Friday, October 17, 2003 5:44 PM
> > > > Subject: RE: Updated COT Trial
> > > >
> > > >
> > > > > Carolyn, Neil,
> > > > > Here is the feedback from the UT-Southwestern site. Almost
> > > everyone
> > > > > is on board and if I can get some good feedback on the
>following
> > > issues
> > > > > I think that this site will be in. There are 3 sticking points
> > as
> > > > > followsn and the fourth point is minor:
> > > > >
> > > > > 1) Complexity of the intervention: Everyone agrees that this
>is
> > a
> > > very
> > > > > complicated study that will be a challenge to do. Most
>everyone
> > is
> > > ready
> > > > > to give it a try at this point but a few are very concerned
> > about
> > > > > feasibilty given that within the ventilation arm of the study,
> > > there are
> > > > > in essence 4 groups (based on the 2 strata), and each has some
> > > specific
> > > > > issues. We would like to offer a potential solution which may
> > > appease
> > > > > many at this and other sites: Consider staging the initiation
>of
> > > the
> > > > > study such that for the first 4-6 months the study only enters
> > > infants
> > > > > in the 26-27 wk strata and subsequently the 24-25 week strata
>is
> > > then
> > > > > initiated. This will allow people to get accustomed to the
>study

> > in
> > > a
> > > > > group which may be more stable and with less problems, and
>take
> > > care of
> > > > > unanticipated problems which invariably will come up (as we
> > > encountered
> > > > > with the SAVE trial). This should help deal with the
>feasibiltiy
> > > issues
> > > > > that so many attendings are concerned about since it will be
> > easier
> > > to
> > > > > focus on 2 groups within the ventilation arm rather than 4.
> > > > > >
> > > > > 2) Re-Intubation Criteria: A number of people expressed
>concern
> > > that
> > > > > re-intubation criteria should have a pH associated with it if
> > > these
> > > > > criteria are to be extended over such a long time interval of
>28
> > > days.
> > > > > For example, at 14-28 days if we had an infant with a well
> > > compensated
> > > > > respiratory acidosis even with a high oxygen requriement, we
> > would
> > > still
> > > > > try to keep the infant off the ventilator. This reflects the
> > > movement of
> > > > > this site to a more permissive strategy for right or wrong
> > reasons.
> > > It
> > > > > is difficult to get people to move from this management (even
> > > though we
> > > > > have no data to say it is right) given that the intervention
> > will
> > > > > prolong time on the ventilator. I thiink I have been
>successful
> > > in
> > > > > getting people to understand that it is critical to have
> > > separation
> > > > > between groups and maybe including a pH will obviate that.
> > However,
> > > some
> > > > > further discussion regarding this issue would benefit our
>site.
> > > > > >
> > > > > 3) Use of surfactant up to 72 hours: We will not give
>surfactant
> > > after
> > > > > 48 hours (we rarely give now after 36 hours) since it does not
> > work
> > > well
> > > > > and we will be wasting the preparation. We are under heavy
> > pressure
> > > to
> > > > > watch our costs and using surfactant at such a late post-natal
> > age
> > > will

> > > > > not sit well with Administration since the study is so
>different
> > > from
> > > > > our practice. If other centers use it at 36-72 hours of age,
> > fine,
> > > but
> > > > > build in a window of time for surfactant use so we don't get
> > dinged
> > > with
> > > > > violations for something we will not do.
> > > > >
> > > > > 4) Type of CPAP: Clarify what type of CPAP will be acceptable
> > for
> > > the
> > > > > study and what type of equipment we will need.
> > > > >
> > > > > Hope this helps. I think this site is moving in the right
> > > direction.
> > > > > Sorry for the late response but by my watch it is still 10/17.
> > AL
> > > > >
> > > > > >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> > > > > Reminder that today is the deadline for your comments:
> > > > >
> > > > >
> > > > > To the Neonatal Research Network Steering Committee:
> > > > >
> > > > > Attached is the latest COT trial for your input. Please send
> > > comments
> > > > > by
> > > > > Friday, October 17.
> > > > >
> > > > > Thanks!
> > > > >
> > > > > Carolyn
> > > > >
> > > > >
> > > > >
> > > > >
> > > > >
> > > >
> > > >
> > >
> > >

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884
Fax 216-844-1479

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Wally Carlo, M.D.
To: "Neil Finer"; ALAN.JOBE@cchmc.org; Higgins, Rosemary (NIH/NICHD)
Cc: Ed Donovan; Avroy A. Fanaroff, M.D.; Higgins, Rosemary (NIH/NICHD); Shahnaz Duara
Subject: RE: COT trial
Date: Saturday, November 08, 2003 3:35:12 AM

Hi Alan and Rose: I also agree. I think this trial addresses important questions but more important may define an important issue regarding the capability of the NRN to do difficult management trials. A good solution may be to limit the trial to those who can do it (as finally modified with a consensus and reviewers' approval). We may loose a few center, but that would be better to having centers that can not do the intervention (which would reduce the chance to see an effect). Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Monday, November 03, 2003 6:24 PM
To: ALAN.JOBE@cchmc.org; higginsr@mail.nih.gov
Cc: Ed Donovan; Avroy A. Fanaroff, M.D.; higginsr@mail.nih.gov; Neil Finer; Shahnaz Duara; Wally Carlo, M.D.
Subject: Fw: COT trial

Hi Alan and Rose
Ed's comments reflect a phone call that held by the Ventilator subgroup. I am very concerned that each center is providing arguments about why the COT trial will not work in their center. We are trying to be compliant, but I have a concern that each center wants to defend current practice more than test another approach.
As an example - lowering the age in hours for which surfactant should be given if intubated still does not sit well with Abbot - His site was the reason for the change. They are the lowest user of surf in the 26-27 week group, and the study will result in a possible further decrease in Surfactant because the Treated infants may not ever qualify to receive surfactant. Their current practice may result in good outcomes but is not evidence based in that prophylactic Surfactant produces the best outcomes. Early surfactant is also associated with better outcomes but these 2 approaches have not been compared.
Our study is not a surfactant study. It is designed to provide the control infants with an evidence based intervention and we will be comparing the use of CPAP and more restrictive criteria. If each site is reluctant to suspend their belief and current practice in an effort to develop evidence, we will never advance our knowledge in multicenter trials.
Indeed more sites practice prophylactic use of surfactant and the average at 26 weeks is that 85% of infants in the Network centers receive this treatment. One could expect that the loudest objections would come from these centers because their practice will undergo dramatic changes for the treatment infants.
I will continue to work with everyone and try to develop an acceptable approach. I am concerned as Ed so clearly expressed that the cup is seen as half empty!!
Regards
Neil
----- Original Message -----
From: Edward Donovan
To: ALAN JOBE ; higginsr@mail.nih.gov
Cc: nfiner@ucsd.edu
Sent: Monday, November 03, 2003 4:53 AM
Subject: COT trial

Rose and Alan,
I am very concerned about this trial. Everyone voted to do the trial, but everyone also voted for SAVE and Surf-CPAP. The COT Subcommittee has had no positive comments from other PIs. We have only received a list of reasons why "it won't work in my center". We need some cheerleading about why this is an important trial for the Network and why we may have to convince our colleagues to "suspend belief" if we are to do a successful trial.

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: CHMCC Groupwise
To: Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT trial
Date: Tuesday, November 04, 2003 7:07:25 AM

I agree with your thoughts – just illustrates how difficult it is to get an already formed group to accept any intervention trial. If you shopped the trial around to other units, there would not be this problem – which solves nothing in terms of this trial. At this point, we probably should wait for the external review to see what they say, and then move ahead. I am willing to write an inspirational piece to motivate the centers, but it may not have much effect – the real problem is that the centerPI's are just voicing the anxieties of their colleagues – the ones who have to do the trial.

Alan H. Jobe, MD, PhD
Professor of Pediatrics
Division of Pulmonary Biology/Neonatology
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue, ML#7029
Cincinnati, Ohio 45229
ph: 513-636-8563
fax: 513-636-8691
E-mail: alan.jobe@cchmc.org

From:	Neil Finer
To:	Abbot Laptook
Cc:	Ed Donovan; Avroy A. Fanaroff, M.D.; Higgins, Rosemary (NIH/NICHD); Neil Finer; Shahnaz Duara; Wally Carlo, M.D.
Subject:	Re: Fw: Updated COT Trial
Date:	Monday, November 03, 2003 8:02:01 PM

Hello Abbot
As you know we have tried to address your concerns. I will try to explain the current methodology.
The protocol does not address the infant (who would be a Control in the 26-27 week arm) who requires intubation in the DR for resus and then does well. We have no way of knowing what percent of infants this represents in the Network. We initially wanted to treat all Control infants in this strata with prophylactic surfactant as this is an evidence based intervention. We were convinced by your practice that this may represent a difficulty with some sites and thus allowed that infants in this strata who do not require aggressive resus and who are able to be maintained on < 30% oxygen would not require surfactant. I believe that overall surfactant use will decrease as the Treatment infants will need to be more compromised than is current practice before they receive surfactant. Overall 85% of infants in the 26 week strata receive surfactant so there is an excellent chance the surfactant use will decrease.
Our study is not a surfactant study. It is designed to provide the control infants with an evidence based intervention and we will be comparing the use of CPAP and more restrictive criteria to early surfactant use. Every site will have to change practice to a greater or lesser degree as the protocol does not represent current practice at any site for the Treatment and Control Infants. Each site will have to suspend their current belief and current practice in an effort to develop evidence as to which intervention is best, or to learn that they are equivalent. We have tried to be as minimally prescriptive as possible, and I hope that your site can participate with enthusiasm.
Thanks for your comments.
Neil

----- Original Message -----
From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
To: <nfiner@ucsd.edu>
Cc: <Edward.Donovan@chmcc.org>; <higginsr@mail.nih.gov>; <sduara@miami.edu>; <WCarlo@PEDS.UAB.EDU>; <aaf2@po.cwru.edu>; "Walid Salhab" <Walid.Salhab@UTSouthwestern.edu>
Sent: Saturday, November 01, 2003 10:44 AM
Subject: Re: Fw: Updated COT Trial

> Neil,
> Sorry I could not get back to you sooner but I have been out of town.
> With regards to your question below of a mandatory use of surfactant for
> infants intubated within 48hr of age (26-27 week strata), we would
> answer that this would not be ok with our site. This type of approach
> does not allow any leeway for infants that are intubated in the delivery
> room for poor respiratory effort, do not have lung disease and are
> weaning and get to room air by an hour of age (we do not give these
> infants surfactant). The protocol as it stands now does not address
> this issue. For the latter infants that are extubated on day 1 but
> develop atelectasis, oxygen requirement and are put back on the

> ventilator at less than 48hr of age, we do not give surfactant. We do
> give surfactant up to 48 hrs of age but this is uncommon. Most is given
> on day 1 and occassionaly up to 36 hours. Abbot
> >>> "Neil Finer" <nfiner@ucsd.edu> 10/27/03 12:47:33 PM >>>
> Abbot
> I tried to call you today, but I missed you. Surfactant will be an
> issue
> only for the 26-27 week treated infants. Would you be OK with a
> mandatory
> use of surfactant if these infants require intubation within 48 hrs of
> birth, and that after that, it is left to the site? This was not
> intended to
> be a study of surfactant in these infants, but rather a safeguard for
> the
> treatment infants who need intubation.
> Neil
> ----- Original Message -----
> From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> To: <nfiner@ucsd.edu>
> Cc: <HigginsR@mail.nih.gov>; "Walid Salhab"
> <Walid.Salhab@UTSouthwestern.edu>
> Sent: Sunday, October 26, 2003 11:07 AM
> Subject: Re: Fw: Updated COT Trial
>
>
> > Neil,
> > These responses are very helpful. With regards to the pH, we
> > presently do not have a firm pH or pCO2 for reintubation when we are
> > dealing with established or clearly evolving BPD. Specifically if we
> had
> > an infant off the ventilator at more than 2 weeks of age, most of us
> > would try to maintain the infant off the ventilator if the pCO2 was
> >55
> > but the pH maintained >7.20-7.25 even with an FiO2 > 50%. I think we
> do
> > realize that we have moved to this strategy without data but what
> drives
> > it is reducing the time on mechanical ventilation. I think your
> > suggestion of using the intubation criteria of the protocol for the
> > first 14 days is very reasonable from our perspective. With regard
> to
> > point 3 and surfactant, what we are concerned with is the initail
> dose
> > of surfactant. We do not use surfactant past 48 hours and rarely use
> it
> > after 36 hours. I am not sure if I am misinterpreting the protocol
> but
> > if an infant ends up on CPAP and 35% O2 at 60 hours of age with
> apnea
> > and atelectasis but never had surfactant previously, they would now
> need
> > to get surfactant. Now that you raise the repeat dosing of
> surfactant
> > above, that should be clarified.
> > I appreciate your response Neil. Abbot
> >
> > >>> "Neil Finer" <nfiner@ucsd.edu> 10/26/03 12:38:39 PM >>>
> >
> > > Hello Abbot
> > > I will try to answer all your questions.

> > > 1) Staging in the 2 Strata. This may be an option, and it may
> help
> > some
> > > sites. We would prefer to start both strata together. The criteria
> > for
> > > intubation and extubation are similar between these strata and
> > actually as
> > > the smaller infants all get prophylactic surfactant, this may be
> > easier to
> > > manage. I will ask RTI if initiated the study at some sites for
> only
> > 1
> > > strata represents a problem. Our Subcommittee is OK with this
> > modification.
> > > 2) We removed pH thinking that the sites were sending the message
> > that we
> > > were too prescriptive. Reintubation is only mandated for the
> Control
> > > Infants, and we can certainly add the pH if you think that this is
> > helpful.
> > > Will your group currently not re-intubate a baby with a PaCO2 > 55
> > and an
> > > Oxygen requirement > 50% if the pH is > 7.25 but would if the pH
> was
> > <
> > 7.25?
> > > What pH are you currently using? Would they accept these criteria
> for
> > the
> > > first 7-14 days?
> > > We could take the position that after the first 7 days
> re-intubation
> > will
> > be
> > > a local decision, and let the protocol separate the infants out by
> > initial
> > > management.
> > > 3) The protocol says that repeat surfactant may be given and does
> > not
> > force
> > > the use of additional doses in either strata. We will ensure that
> > this
> > > message is clearly stated in the final protocol and study manual.
> > > 4) Any form of CPAP may be used. We are hopeful that the bubble
> CPAP
> > may
> > be
> > > available by the time of the study initiation, but is has yet to
> > receive
> > FDA
> > > approval.
> > > I hope that these responses are helpful.
> > > Neil
> > > ----- Original Message -----
> > > From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> > > To: <petrie@rti.org>; <nfiner@ucsd.edu>
> > > Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>; "Walid
> > Salhab"
> > > <Walid.Salhab@UTSouthwestern.edu>
> > > Sent: Friday, October 17, 2003 5:44 PM

> > > Subject: RE: Updated COT Trial
> > >
> > >
> > > > Carolyn, Neil,
> > > > Here is the feedback from the UT-Southwestern site. Almost
> > everyone
> > > > is on board and if I can get some good feedback on the following
> > issues
> > > > I think that this site will be in. There are 3 sticking points
> as
> > > > followsn and the fourth point is minor:
> > > >
> > > > 1) Complexity of the intervention: Everyone agrees that this is
> a
> > very
> > > > complicated study that will be a challenge to do. Most everyone
> is
> > ready
> > > > to give it a try at this point but a few are very concerned
> about
> > > > feasibilty given that within the ventilation arm of the study,
> > there are
> > > > in essence 4 groups (based on the 2 strata), and each has some
> > specific
> > > > issues. We would like to offer a potential solution which may
> > appease
> > > > many at this and other sites: Consider staging the initiation of
> > the
> > > > study such that for the first 4-6 months the study only enters
> > infants
> > > > in the 26-27 wk strata and subsequently the 24-25 week strata is
> > then
> > > > initiated. This will allow people to get accustomed to the study
> in
> > a
> > > > group which may be more stable and with less problems, and take
> > care of
> > > > unanticipated problems which invariably will come up (as we
> > encountered
> > > > with the SAVE trial). This should help deal with the feasibiltiy
> > issues
> > > > that so many attendings are concerned about since it will be
> easier
> > to
> > > > focus on 2 groups within the ventilation arm rather than 4.
> > > > >
> > > > 2) Re-Intubation Criteria: A number of people expressed concern
> > that
> > > > re-intubation criteria should have a pH associated with it if
> > these
> > > > criteria are to be extended over such a long time interval of 28
> > days.
> > > > For example, at 14-28 days if we had an infant with a well
> > compensated
> > > > respiratory acidosis even with a high oxygen requriement, we
> would
> > still
> > > > try to keep the infant off the ventilator. This reflects the
> > movement of
> > > > this site to a more permissive strategy for right or wrong

> reasons.
> > It
> > > > is difficult to get people to move from this management (even
> > though we
> > > > have no data to say it is right) given that the intervention
> will
> > > > prolong time on the ventilator. I thiink I have been successful
> > in
> > > > getting people to understand that it is critical to have
> > separation
> > > > between groups and maybe including a pH will obviate that.
> However,
> > some
> > > > further discussion regarding this issue would benefit our site.
> > > >
> > > > 3) Use of surfactant up to 72 hours: We will not give surfactant
> > after
> > > > 48 hours (we rarely give now after 36 hours) since it does not
> work
> > well
> > > > and we will be wasting the preparation. We are under heavy
> pressure
> > to
> > > > watch our costs and using surfactant at such a late post-natal
> age
> > will
> > > > not sit well with Administration since the study is so different
> > from
> > > > our practice. If other centers use it at 36-72 hours of age,
> fine,
> > but
> > > > build in a window of time for surfactant use so we don't get
> dinged
> > with
> > > > violations for something we will not do.
> > > >
> > > > 4) Type of CPAP: Clarify what type of CPAP will be acceptable
> for
> > the
> > > > study and what type of equipment we will need.
> > > >
> > > > Hope this helps. I think this site is moving in the right
> > direction.
> > > > Sorry for the late response but by my watch it is still 10/17.
> AL
> > > >
> > > > >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> > > > Reminder that today is the deadline for your comments:
> > > >
> > > >
> > > > To the Neonatal Research Network Steering Committee:
> > > >
> > > > Attached is the latest COT trial for your input. Please send
> > comments
> > > > by
> > > > Friday, October 17.
> > > >
> > > > Thanks!
> > > >
> > > > Carolyn

> > > >
> > > >
> > > >
> > > >
> > >
> > >
> >
> >
>

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: ALAN JOBE
Subject: Fwd: Re: Fw: Updated COT Trial
Date: Monday, November 03, 2003 7:56:12 AM
Attachments: Re Fw Updated COT Trial.msg

We are having the same problem that we had with SAVE and the Surf-CPAP study, i.e. that the protocol doesn't "fit current practice". I don't know how to do it, but somehow we need to share the message that clinical trials require "suspension of belief" in what we think is the right thing to do. Otherwise, why are we in a trials group?
Ed

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

From: Neil Finer
To: Edward Donovan
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: COT Trial
Date: Wednesday, October 29, 2003 11:51:04 AM

Thanks Ed
I thought that should would encourage DR use. but I can live with anything. Richard thought that more pressure for early use would be better.
I am trying to get adherence to the protocol for as long as possible. Do you think that after 14 days, the vent management will make a large difference - I tend to believe that the die is already cast. Would you want to go for 28 days?
Thanks
Neil

----- Original Message -----
From: Edward Donovan
To: higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
Sent: Tuesday, October 28, 2003 2:45 PM
Subject: Re: COT Trial

Neil,
1. The 500 gram cutoff is ok by me.
2. I don't understand what we lose by keeping the intervention going longer? It seems to me that once clinicians are into a given ventilation mode for a given infant, it wouldn't be too difficult to keep going.
3. It's either 'must give in DR' or 'must give before 1 hr'. "Should" gives clinicians the opportunity to do what they choose. I favor "before 1 hr." because this allows flexibility - in the absence of evidence that 10 min is better and safer than 1 hr.
4. ok
5. 0.3 may be a hard swallow for our group, but we will comply.

Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 10/28/2003 2:19:20 PM >>>
Hello Everyone
I am writing from my soot filled office, and it looks like Tokyo with everyone wearing masks.
Hopefully the fires will soon be under control.
I am attaching a revision of the Ventilation portion of the protocol. I would like to make a number of changes as detailed below, which are in this version.
1) Include in the 24 -25 week stratum only infants of ≥ 500gm. I believe that all infants below 500 will fail early extubation, and this group has a survival of 16% based on the Network data.
2). Change the duration of the active protocol to 14 days. This may blur the differences, but in a discussion with Richard, he felt that this would be a good move.
3). Reword the Control intervention for the 26-27 week stratum to say that these infants SHOULD be

intubated and receive prophylactic surfactant, but may have this delayed till one hour. I have changed the criteria for such intubation to be an FiO2 > .30 with or without CPAP, thus simplifying this intervention. It was our intent to have this group receive prophylaxis, but Abbot was concerned. The current draft will still allow the 1 hour window, but more strongly supports the earlier intervention in the DR.

4). I have included criteria for hemodynamic instability and used these in the criteria.

5). I have changed the criteria for FiO2 for reintubation of control infants to read as follows: An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life

I have highlighted all changes.

Please review and send me your thoughts/changes. The protocol now needs to go out for external review, and then we are good to go if these reviews are OK.

Thanks for all your input.

Once I have heard from you, I will give the protocol to Rose for external review.

Be well

Neil

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: COT Trial
Date: Wednesday, October 29, 2003 10:01:38 AM

---

agree

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> 10/28/2003 6:24:27 PM >>>
Neil: I am ok with everything except intubation if FiO2 is more than 30 in the first 72 h or more than 50 after 72 h. I am concerned that this is more aggresive ventilation than usual and I would rather have the intervention be a more conservative approach to the experimental group rather than more aggressive ventilation of the control group. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 28, 2003 1:19 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: COT Trial

Hello Everyone
I am writing from my soot filled office, and it looks like Tokyo with everyone wearing masks. Hopefully the fires will soon be under control.
I am attaching a revision of the Ventilation portion of the protocol. I would like to make a number of changes as detailed below, which are in this version.
1) Include in the 24 -25 week stratum only infants of ≥ 500gm. I believe that all infants below 500 will fail early extubation, and this group has a survival of 16% based on the Network data.
2). Change the duration of the active protocol to 14 days. This may blur the differences, but in a discussion with Richard, he felt that this would be a good move.
3). Reword the Control intervention for the 26-27 week stratum to say that these infants SHOULD be intubated and receive prophylactic surfactant, but may have this delayed till one hour. I have changed the criteria for such intubation to be an FiO2 > .30 with or without CPAP, thus simplifying this intervention. It was our intent to have this group receive prophylaxis, but Abbot was concerned. The current draft will still allow the 1 hour window, but more strongly supports the earlier intervention in the DR.
4). I have included criteria for hemodynamic instability and used these in the criteria.
5). I have changed the criteria for FiO2 for reintubation of control infants to read as follows: An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life
I have highlighted all changes.
Please review and send me your thoughts/changes. The protocol now needs to go out for external review, and then we are good to go if these reviews are OK.
Thanks for all your input.
Once I have heard from you, I will give the protocol to Rose for external review.
Be well
Neil

From: Wally Carlo, M.D.
To: "Neil Finer"; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial
Date: Wednesday, October 29, 2003 7:57:43 AM

I think we can live with >40 and 14 days to keep it simple. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, October 28, 2003 9:51 PM
To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: COT Trial

Hi All -
Shahnaz and Wally
You are correct. I have changed the reintubation criteria to an FiO2 > .40 and have left this for the 14 day duration. What do you think of higher PaCO2 and FiO2 after 14 days as Shahnaz suggests or just leaving the criteria for 14 days? Do we need to be prescriptive after 14 days?
Thanks for the rapid feed back.
Be well
Neil

----- Original Message -----
From: Neil Finer
To: Wally Carlo, M.D. ; Shahnaz Duara ; Neil Finer ; higginsr@mail.nih.gov ; Avroy A. Fanaroff, M.D. ; Ed Donovan
Sent: Tuesday, October 28, 2003 11:19 AM
Subject: COT Trial

Hello Everyone
I am writing from my soot filled office, and it looks like Tokyo with everyone wearing masks. Hopefully the fires will soon be under control.
I am attaching a revision of the Ventilation portion of the protocol. I would like to make a number of changes as detailed below, which are in this version.
1) Include in the 24 -25 week stratum only infants of ≥ 500gm. I believe that all infants below 500 will fail early extubation, and this group has a survival of 16% based on the Network data.
2). Change the duration of the active protocol to 14 days. This may blur the differences, but in a discussion with Richard, he felt that this would be a good move.
3). Reword the Control intervention for the 26-27 week stratum to say that these infants SHOULD be intubated and receive prophylactic surfactant, but may have this delayed till one hour. I have changed the criteria for such intubation to be an FiO2 > .30 with or without CPAP, thus simplifying this intervention. It was our intent to have this group receive prophylaxis, but Abbot was concerned. The current draft will still allow the 1 hour window, but more strongly supports the earlier intervention in the DR.
4). I have included criteria for hemodynamic instability and used these in the criteria.
5). I have changed the criteria for FiO2 for reintubation of control infants to read as follows:
An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life
I have highlighted all changes.
Please review and send me your thoughts/changes. The protocol now needs to go out for external review, and then we are good to go if these reviews are OK.
Thanks for all your input.
Once I have heard from you, I will give the protocol to Rose for external review.
Be well
Neil

From: Avroy A. Fanaroff
To: Shahnaz Duara; "Wally Carlo, M.D."; "Neil Finer"; Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff, M.D."; "Ed Donovan"
Subject: RE: COT Trial
Date: Tuesday, October 28, 2003 11:12:10 PM

Hi
sad but true, we are coming close to consensus
I strongly agree with the cut off of 500 grams and we could even make a case for 600 grams but I would be pushing my luck.
I like the window for surfactant and have no strong feelings on the criteria for reintubation or duration of trial
My strong feelings are that the trial must go forward.
Av
At 08:22 PM 10/28/2003 -0500, Shahnaz Duara wrote:

> Hi Neil,
> 1. I am OK with the 500 g cut-off also.
> 2. Length of trial: I can see why Richard wanted a 14 day cut-off - beyond that, the protocol could be criticised because we are using the same re-intubation parameters for both 'acute' and 'chronic' babies. One approach could be to have higher PaCO2 and FiO2 levels for re-intubation beyond 14 days, similar idea to the higher bili levels for re-starting bililights in the phototherapy study, day 8 on.
> 3. Allowing the 1 hr window for surfactant in the control gp 26-27 weeks is OK
> 4. The hemodynamic stuff is OK
> 5. The FiO2 of 0.3 for re-intubation in the control group is a little problematic. I agree with Wally that beyond 72 hours, there may be opposition to the 0.3. Also, this will make for inconsistency with our extubation criteria in the control arm - if an FiO2 of 0.4 is what we accept for extubation, how can we re-intubate at 0.3? If you want to stick to 0.3, are you planning to propose an FiO2 <0.3 for control gp extubation?
>
> Shahnaz
>
> > -----Original Message-----
> > From: Wally Carlo, M.D. [mailto:WCarlo@PEDS.UAB.EDU]
> > Sent: Tuesday, October 28, 2003 6:24 PM
> > To: 'Neil Finer'; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
> > Subject: RE: COT Trial
> >
> > Neil: I am ok with everything except intubation if FiO2 is more than 30 in the first 72 h or more than 50 after 72 h. I am concerned that this is more aggresive ventilation than usual and I would rather have the intervention be a more conservative approach to the experimental group rather than more aggressive ventilation of the control group. Wally
> > -----Original Message-----
> > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > Sent: Tuesday, October 28, 2003 1:19 PM
> > To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
> > Subject: COT Trial
> >
> > Hello Everyone
> > I am writing from my soot filled office, and it looks like Tokyo with everyone wearing masks. Hopefully the fires will soon be under control.
> > I am attaching a revision of the Ventilation portion of the protocol. I would like to

make a number of changes as detailed below, which are in this version.
1) Include in the 24 -25 week stratum only infants of > 500gm. I believe that all infants below 500 will fail early extubation, and this group has a survival of 16% based on the Network data.
2). Change the duration of the active protocol to 14 days. This may blur the differences, but in a discussion with Richard, he felt that this would be a good move.
3). Reword the Control intervention for the 26-27 week stratum to say that these infants SHOULD be intubated and receive prophylactic surfactant, but may have this delayed till one hour. I have changed the criteria for such intubation to be an FiO2 > .30 with or without CPAP, thus simplifying this intervention. It was our intent to have this group receive prophylaxis, but Abbot was concerned. The current draft will still allow the 1 hour window, but more strongly supports the earlier intervention in the DR.
4). I have included criteria for hemodynamic instability and used these in the criteria.
5). I have changed the criteria for FiO2 for reintubation of control infants to read as follows: An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life
I have highlighted all changes.
Please review and send me your thoughts/changes. The protocol now needs to go out for external review, and then we are good to go if these reviews are OK.
Thanks for all your input.
Once I have heard from you, I will give the protocol to Rose for external review.
Be well
Neil

TREATMENT Group : Early Extubation and CPAP
Protocol:

Treatment Group – Delivery Room Management: 24 – 25 weeks Stratum (≥ 500 gm birth weight). Infants will be intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth. These infants will be extubated by 1 hour of age if they fulfill the criteria below for Extubation.

This approach will provide the more immature strata infants with the benefit of prophylactic or early surfactant

Treatment Infants - NICU Management: 24 - 25 weeks

All Intubated Treatment infants of 24-25 wks stratum ***must*** be extubated by 1 hour of age, if they meet the Criteria for Extubation, as outlined below. These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention

Extubation Criteria for 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.

Following extubation, 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 5-6 cm H20 or nasal SIMV.

Subsequent Intubation Criteria for Treatment infants

Intubation ***May BE attempted 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 low blood pressure and/or poor perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for 14 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, for example a higher FiO_2.***

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 – 20 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.

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.

Delivery Room Management : Treatment Group – 26-27 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 MAY be intubated and given surfactant (within the first 72 hours of life)

- An FiO_2 >.50 to maintain an indicated SpO2 $\geq$ 90% (using the altered Pulse Oximeters)
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous

subtract 5 torr from PCO2)
- Hemodynamic instability defined as a low blood pressure and/or poor perfusion, requiring volume and/or pressor support.

These criteria will continue in effect for 14 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

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, 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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable

These criteria will continue in effect for 14 days from birth.

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.***

<u>CONTROL Group: Prophylactic Surfactant and Ventilation Overview:</u>

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 24-25 wk strata, and ***should*** be used for Control infants of 26-27 week infants. Any Control infant who has not received prophylactic surfactant in the DR, will receive surfactant within the first 48 hours of life if they subsequently meet intubation criteria. Surfactant may be given to these infants after 48 hours, but will not be mandated by the protocol.

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.

Control Group - NICU Management: 24 – 25 weeks strata

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

Extubation Criteria for Intubated Control Group infants: 24 – 25 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr and/or pH > 7.25(arterial or capillary samples, if venous subtract 5 torr from PCO2)
- 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.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in some centers. There are currently no standard criteria for extubation of such infants. 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 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life

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.
We have also added a 4 hour minimal window to allow for some flexibility.)

Control Group – Delivery Room Management : 26 – 27 weeks Stratum:
Infants ***should*** 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 $\geq$ 90% with or without CPAP using study oximeter
- A $PaCO_2$ > 55 torr (Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1 (arterial or capillary samples, if venous subtract 5 torr from PCO2)

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 not allow the use of CPAP and > 30% oxygen within the first 72 hours of life for any control infant who has not been intubated and received surfactant.

Extubation Criteria for Intubated Control Group infants: 26 – 27 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) with a pH > 7.25
- 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.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

Re-intubation or Initial Intubation Criteria for Control Infants 26 – 27 weeks: Non-intubated Control Infants meeting all 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)
- pH < 7.25
- An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters for the first 72 hours of life, and > .50 after the first 72 hours of life.

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 is not required by the study protocol.

From: Wally Carlo, M.D.
To: "Edward Donovan"; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: COT Trial
Date: Tuesday, October 28, 2003 6:33:51 PM

I agree with Ed that keeping the intervention longer should be better and acceptable to most. I would not design the protocol for the least common denominator. Wally

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Tuesday, October 28, 2003 4:45 PM
To: higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: Re: COT Trial

Neil,
1. The 500 gram cutoff is ok by me.
2. I don't understand what we lose by keeping the intervention going longer? It seems to me that once clinicians are into a given ventilation mode for a given infant, it wouldn't be too difficult to keep going.
3. It's either 'must give in DR' or 'must give before 1 hr'. "Should" gives clinicians the opportunity to do what they choose. I favor "before 1 hr." because this allows flexibility - in the absence of evidence that 10 min is better and safer than 1 hr.
4. ok
5. 0.3 may be a hard swallow for our group, but we will comply.

Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 10/28/2003 2:19:20 PM >>>
Hello Everyone
I am writing from my soot filled office, and it looks like Tokyo with everyone wearing masks. Hopefully the fires will soon be under control.
I am attaching a revision of the Ventilation portion of the protocol. I would like to make a number of changes as detailed below, which are in this version.
1) Include in the 24 -25 week stratum only infants of ≥ 500gm. I believe that all infants below 500 will fail early extubation, and this group has a survival of 16% based on the Network data.
2). Change the duration of the active protocol to 14 days. This may blur the differences, but in a discussion with Richard, he felt that this would be a good move.
3). Reword the Control intervention for the 26-27 week stratum to say that these infants SHOULD be intubated and receive prophylactic surfactant, but may have this delayed till one hour. I have changed the criteria for such intubation to be an FiO2 > .30 with or without CPAP, thus simplifying this intervention. It was our intent to have this group receive prophylaxis, but Abbot was concerned. The current draft will still allow the 1 hour window, but more strongly supports the earlier intervention in the DR.
4). I have included criteria for hemodynamic instability and used these in the criteria.
5). I have changed the criteria for FiO2 for reintubation of control infants to read as follows: An FiO2 > .30 with or without CPAP with a SpO2 < 90% using the study pulse oximeters

for the first 72 hours of life, and > .50 after the first 72 hours of life
I have highlighted all changes.
Please review and send me your thoughts/changes. The protocol now needs to go out for external review, and then we are good to go if these reviews are OK.
Thanks for all your input.
Once I have heard from you, I will give the protocol to Rose for external review.
Be well
Neil

From:	Neil Finer
To:	Abbot Laptook
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: Fw: Updated COT Trial
Date:	Monday, October 27, 2003 1:47:43 PM

Abbot
I tried to call you today, but I missed you. Surfactant will be an issue only for the 26-27 week treated infants. Would you be OK with a mandatory use of surfactant if these infants require intubation within 48 hrs of birth, and that after that, it is left to the site? This was not intended to be a study of surfactant in these infants, but rather a safeguard for the treatment infants who need intubation.
Neil
----- Original Message -----
From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
To: <nfiner@ucsd.edu>
Cc: <HigginsR@mail.nih.gov>; "Walid Salhab" <Walid.Salhab@UTSouthwestern.edu>
Sent: Sunday, October 26, 2003 11:07 AM
Subject: Re: Fw: Updated COT Trial

> Neil,
> These responses are very helpful. With regards to the pH, we
> presently do not have a firm pH or pCO2 for reintubation when we are
> dealing with established or clearly evolving BPD. Specifically if we had
> an infant off the ventilator at more than 2 weeks of age, most of us
> would try to maintain the infant off the ventilator if the pCO2 was >55
> but the pH maintained >7.20-7.25 even with an FiO2 > 50%. I think we do
> realize that we have moved to this strategy without data but what drives
> it is reducing the time on mechanical ventilation. I think your
> suggestion of using the intubation criteria of the protocol for the
> first 14 days is very reasonable from our perspective. With regard to
> point 3 and surfactant, what we are concerned with is the initail dose
> of surfactant. We do not use surfactant past 48 hours and rarely use it
> after 36 hours. I am not sure if I am misinterpreting the protocol but
> if an infant ends up on CPAP and 35% O2 at 60 hours of age with apnea
> and atelectasis but never had surfactant previously, they would now need
> to get surfactant. Now that you raise the repeat dosing of surfactant
> above, that should be clarified.
> I appreciate your response Neil. Abbot
>
> >>> "Neil Finer" <nfiner@ucsd.edu> 10/26/03 12:38:39 PM >>>
>
> > Hello Abbot
> > I will try to answer all your questions.
> > 1) Staging in the 2 Strata. This may be an option, and it may help
> some
> > sites. We would prefer to start both strata together. The criteria
> for
> > intubation and extubation are similar between these strata and
> actually as
> > the smaller infants all get prophylactic surfactant, this may be
> easier to
> > manage. I will ask RTI if initiated the study at some sites for only
> 1

> > strata represents a problem. Our Subcommittee is OK with this
> modification.
> > 2) We removed pH thinking that the sites were sending the message
> that we
> > were too prescriptive. Reintubation is only mandated for the Control
> > Infants, and we can certainly add the pH if you think that this is
> helpful.
> > Will your group currently not re-intubate a baby with a PaCO2 > 55
> and an
> > Oxygen requirement > 50% if the pH is > 7.25 but would if the pH was
> <
> 7.25?
> > What pH are you currently using? Would they accept these criteria for
> the
> > first 7-14 days?
> > We could take the position that after the first 7 days re-intubation
> will
> be
> > a local decision, and let the protocol separate the infants out by
> initial
> > management.
> > 3) The protocol says that repeat surfactant may be given and does
> not
> force
> > the use of additional doses in either strata. We will ensure that
> this
> > message is clearly stated in the final protocol and study manual.
> > 4) Any form of CPAP may be used. We are hopeful that the bubble CPAP
> may
> be
> > available by the time of the study initiation, but is has yet to
> receive
> FDA
> > approval.
> > I hope that these responses are helpful.
> > Neil
> > ----- Original Message -----
> > From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> > To: <petrie@rti.org>; <nfiner@ucsd.edu>
> > Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>; "Walid
> Salhab"
> > <Walid.Salhab@UTSouthwestern.edu>
> > Sent: Friday, October 17, 2003 5:44 PM
> > Subject: RE: Updated COT Trial
> >
> >
> > > Carolyn, Neil,
> > > Here is the feedback from the UT-Southwestern site. Almost
> everyone
> > > is on board and if I can get some good feedback on the following
> issues
> > > I think that this site will be in. There are 3 sticking points as
> > > followsn and the fourth point is minor:
> > >
> > > 1) Complexity of the intervention: Everyone agrees that this is a
> very
> > > complicated study that will be a challenge to do. Most everyone is
> ready
> > > to give it a try at this point but a few are very concerned about
> > > feasibilty given that within the ventilation arm of the study,

> there are
> > > in essence 4 groups (based on the 2 strata), and each has some
> specific
> > > issues. We would like to offer a potential solution which may
> appease
> > > many at this and other sites: Consider staging the initiation of
> the
> > > study such that for the first 4-6 months the study only enters
> infants
> > > in the 26-27 wk strata and subsequently the 24-25 week strata is
> then
> > > initiated. This will allow people to get accustomed to the study in
> a
> > > group which may be more stable and with less problems, and take
> care of
> > > unanticipated problems which invariably will come up (as we
> encountered
> > > with the SAVE trial). This should help deal with the feasibiltiy
> issues
> > > that so many attendings are concerned about since it will be easier
> to
> > > focus on 2 groups within the ventilation arm rather than 4.
> > >
> > > 2) Re-Intubation Criteria: A number of people expressed concern
> that
> > > re-intubation criteria should have a pH associated with it if
> these
> > > criteria are to be extended over such a long time interval of 28
> days.
> > > For example, at 14-28 days if we had an infant with a well
> compensated
> > > respiratory acidosis even with a high oxygen requriement, we would
> still
> > > try to keep the infant off the ventilator. This reflects the
> movement of
> > > this site to a more permissive strategy for right or wrong reasons.
> It
> > > is difficult to get people to move from this management (even
> though we
> > > have no data to say it is right) given that the intervention will
> > > prolong time on the ventilator. I thiink I have been successful
> in
> > > getting people to understand that it is critical to have
> separation
> > > between groups and maybe including a pH will obviate that. However,
> some
> > > further discussion regarding this issue would benefit our site.
> > >
> > > 3) Use of surfactant up to 72 hours: We will not give surfactant
> after
> > > 48 hours (we rarely give now after 36 hours) since it does not work
> well
> > > and we will be wasting the preparation. We are under heavy pressure
> to
> > > watch our costs and using surfactant at such a late post-natal age
> will
> > > not sit well with Administration since the study is so different
> from
> > > our practice. If other centers use it at 36-72 hours of age, fine,
> but

> > > build in a window of time for surfactant use so we don't get dinged
> with
> > > violations for something we will not do.
> > >
> > > 4) Type of CPAP: Clarify what type of CPAP will be acceptable for
> the
> > > study and what type of equipment we will need.
> > >
> > > Hope this helps. I think this site is moving in the right
> direction.
> > > Sorry for the late response but by my watch it is still 10/17. AL
> > >
> > > >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> > > Reminder that today is the deadline for your comments:
> > >
> > >
> > > To the Neonatal Research Network Steering Committee:
> > >
> > > Attached is the latest COT trial for your input. Please send
> comments
> > > by
> > > Friday, October 17.
> > >
> > > Thanks!
> > >
> > > Carolyn
> > >
> > >
> > >
> > >
> >
> >
>
>

From:	Neil Finer
To:	Abbot Laptook
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan; barbara_stoll@oz.ped.emory.edu
Subject:	Re: Updated COT Trial
Date:	Friday, October 24, 2003 12:55:21 PM

Abbot and Barbara
I am OK with staggered enrollment. Are you OK with this trial if a staggered enrollment is allowed?
Many thanks
Neil
----- Original Message -----
From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
To: <ALAN.JOBE@cchmc.org>; <Edward.Donovan@cchmc.org>; <aaf2@cwru.edu>; <jlemons@iupui.edu>; <goldb008@mc.duke.edu>; <sshankar@med.wayne.edu>; <sduara@miami.edu>; <barbara_stoll@oz.ped.emory.edu>; <wcarlo@peds.uab.edu>; <petrie@rti.org>; <dstevenson@stanford.edu>; <nfiner@ucsd.edu>; <dale_phelps@urmc.rochester.edu>; <Jon.E.Tyson@uth.tmc.edu>; <moshea@wfubmc.edu>; <WOh@wihri.org>; <richard.ehrenkranz@yale.edu>
Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>; "Walid Salhab" <Walid.Salhab@UTSouthwestern.edu>
Sent: Thursday, October 23, 2003 1:29 PM
Subject: RE: Updated COT Trial

> To all
> We have less concerns regarding the oxygenation arm since it should
> be transparent to the provider at the bedside, has safety features built
> in, and it certainly has unique design features for studying oxygenation
> as assessed by pulse oximetry. We do share all the concerns regarding
> the complexity of the ventilation arm and have offered a suggestion
> which may make it more feasible to get this study off the ground once
> all the details are worked out; ie consider initiaing the study in
> stages. The study could start with just the 26-27 week strata for the
> first 4 months to identify problems that could not be anticipated and
> allow people in the units to deal with treatment guidelines for only 2
> groups. Once we are on firm grounds with this strata, extend the study
> to the 24-25 wk infants and hopefully this will facilitate keeping all
> study requirements straight. AL
>
> >>> "William Oh" <WOh@wihri.org> 10/23/03 12:24:18 PM >>>
> Hi everyone: In a meeting today, I went over the protocol one more
> time
> with my faculty and fellows. There is a lot of concerns regarding the
> oxygenation arms of the protocol.The specific concerns include the
> high
> range of oxygen target (95%), nursing unable to use pulse oximeter
> for
> clinical monitoring, ust to name a few. While I support the study as I
> have indicated previously, I would appreciate the Committee's serious
> consideration for a trial that involves the CPAP arm only.
>
> Thanks
>
>
> Bill
>

> William Oh, MD
> Professor of Pediatrics
> Brown Medical School
> Attending Neonatologist
> Women and Infants' Hospital
> Providence RI 02905
> Phone (Office) 1 401 274 1122 ext.1432
> (Fax) 1 401 453 7571
>
>
> >>> "Seetha Shankaran M.D" <sshankar@med.wayne.edu> 10/23/03 11:55AM
> >>>
> Hi all
> Yes, I had questioned the primary outcomes , need for separate arms of
> the
> study, and suggested sequential studies rather than factorial design.
> I
> do
> believe the COT committee has worked very hard at addressing issues
> raised.
> I support the study, knowing this will be a bear of a study to do. I
> believe the external reviews will be very helpful to us and look
> forward to
> seeing them. Sometimes we cannot see the forest for the trees.
> I have asked the committee to also study biochemical evidence of
> oxygen
>
> toxicity (such as Vento's work on reduced to oxidized glutathione
> ratios
> in term infants resuscitated with 100% oxygen).
> These discussions are very useful
> Thanks for sharing
> Seetha
>
>
>
> At 04:18 PM 10/22/03 -0400, Edward Donovan wrote:
> >Yes, but.
> >We did enroll "under duress" in the pilot with some success.
> >The SAVE trial was factorial and I think the consent rate and
> enrollment
> >rate were similar to our other simpler trials.
> >We are told that we are funded to do the trials that cannot be done
> by
>
> >less sophisticated groups.
> >This is a difficult and expensive trial, I agree. But, with the
> >resources, we should be able to do it.
> >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
> ><http://www.cprc-chmc.uc.edu>www.cprc-chmc.uc.edu
> >

> > >>> "Lemons, James A" <jlemons@iupui.edu> 10/20/2003 5:29:03 PM >>>
> >We still believe this is going to be an extremely difficult trial to
> >implement and complete. This is due to the complexity of
> incorporating
> >two separate trials with two separate primary outcomes into a singe
> >factorial designed studey (for which the rationale is still unclear),
> as
> >well as the short window for consenting. As challenging as
> enrollment
> has
> >been for phototherapy because of the narrower window, enrollment for
> this
> >trial will be extraordinarily challenging as the window is even
> >tighter. And explaining this complex trial with two separate studies
> to
> >parents under duress will require that much more time. This will be
> >compounded for large centers with multiple sites and many more people
>
> >involved. While we will attempt to support this trial if approved by
> the
> >Steering Committe and outside reviewers, the logistical challenges of
>
> >implementing and enrolling at reasonable rates we perceive as
> extremely
> >difficult.
> > Thanks, Jim
> >-----Original Message-----
> >From: Petrie, Carolyn [mailto:petrie@rti.org]
> >Sent: Friday, October 17, 2003 1:27 PM
> >To: 'M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu)'; 'M. D.
> Alan
> >Jobe (Jobea0@chmcc.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)';
> >Lemons, James A; '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)';
>
> >'Seetha Shankaran (sshankar@med.wayne.edu)'; 'William Oh2
> (WOh@wihri.org)'
> >Cc: 'aRose Higgins (higginsr@mail.nih.gov)'; Hastings, Betty J.;
> Petrie,
> >Carolyn; Poole, W. Kenneth
> >Subject: RE: Updated COT Trial
> >
> >Reminder that today is the deadline for your comments:
> >To the Neonatal Research Network Steering Committee:
> >Attached is the latest COT trial for your input. Please send
> comments
> by
> >Friday, October 17.
> >Thanks!

> >Carolyn
> >
>
>
>
> Seetha Shankaran, MD
> Professor of Pediatrics
> Director, Neonatal-Perinatal Medicine
> Wayne State University School of Medicine
> (313) 745-1436
> sshankar@med.wayne.edu

From: Wally Carlo, M.D.
To: "Neil Finer"
Cc: Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Updated COT Trial
Date: Friday, October 24, 2003 11:33:50 AM

The target in SAVE was a difference no smaller than 5 (<48 vs >52). One would have expected that averaging >5 per patient would give an average differnce relatively much higher than 5. Well, the difference was 4. To give you an idea, the difference was 7 in our pilot work. Our recent trial just stopped (because of lack of diff) after an interin analysis had NO difference (essentially)! Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Friday, October 24, 2003 10:06 AM
To: Wally Carlo, M.D.
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: Updated COT Trial

Wally
What was the problem with SAVE - Was there too little difference in the PaCO2 targets. Do you want another phone call - if so when Neil
----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
To: "Neil Finer" <nfiner@ucsd.edu>; <DONOVAEF@UCMAIL.UC.EDU>; "Shahnaz Duara" <sduara@miami.edu>; <aaf2@cwru.edu>
Sent: Friday, October 24, 2003 5:11 AM
Subject: FW: Updated COT Trial

> Neil et al. : Richard's concern of making sure we can distinguish the
> ventilator management between the groups enough is important. This was
> the main problem in SAVE and has been the problem in two other vent
> trials we have done recently, one that we be submitted now and one
> that we have just stopped. The problem is that as clinicians becomes
> believers in the experimental therapy, there is a lot of
> contamination. We may want to discuss this further among ourselves.
> wally
>
> -----Original Message-----
> From: Richard A Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
> Sent: Thursday, October 23, 2003 6:22 PM
> To: Jon.E.Tyson@uth.tmc.edu; 'Barbara Stoll'; 'Abbot Laptook'
> Cc: ALAN.JOBE@cchmc.org; Edward.Donovan@cchmc.org; aaf2@cwru.edu;
> jlemons@iupui.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu;
> sduara@miami.edu; Wally Carlo, M.D.; petrie@rti.org;
> dstevenson@stanford.edu; nfiner@ucsd.edu;
> dale_phelps@urmc.rochester.edu; Tyson Jon E; moshea@wfubmc.edu;
> WOh@wihri.org; higginsr@mail.nih.gov; bkh@rti.org; poo@rti.org; 'Walid
> Salhab'
> Subject: RE: Updated COT Trial
>
>
> I have been finding the ongoing discussion about this protocol
> fascinating. Similar to Abbot's comment, our group has had little

> difficulty with the pulse oximetry arm of the proposed trial.
> However, given the practice variation that exists between our centers,
> and the narrow differences between the proposed criteria for
> extubation and re-intubation and the ability to treat the control
> 26-27 wk infants with CPAP in the DR if that is a center's current
> resuscitation practice, I think that we are designing a trial that
> will not be capable of
identifying
> any difference between the study groups in the ventilation arm.
> Furthermore, we wonder about the potential for manipulating FiO2
and
> ventilator settings to comply with the preference of the team rather
> than the protocol. I am beginning to think that a better trial would
> be to use the Benchmark trial outcomes, assuming that "best or better
> practices" are identified, at all centers and randomize infants to the
> pulse oximetry intervention.
>
> Richard
>
> At 04:00 PM 10/23/2003 -0500, Jon E Tyson wrote:
>
> >Abbot, would this be a pilot? If so, a pilot would have the
> >disadvantage that the results would perhaps not be properly included
> >in the results of the trial. However, a pilot would have a major
> >advantage if unanticipated problems were found and design
> >modifications, suspension, or even study termination were necessary.
> >In any case, it might be good to predefine criteria for adequate
> >enrollment and compliance during at least this phase.
> >
> >-----Original Message-----
> >From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
> >Sent: Thursday, October 23, 2003 3:39 PM
> >To: Abbot Laptook
> >Cc: ALAN.JOBE@cchmc.org; Edward.Donovan@cchmc.org; aaf2@cwru.edu;
> >jlemons@iupui.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu;
> >sduara@miami.edu; wcarlo@peds.uab.edu; petrie@rti.org;
> >dstevenson@stanford.edu; nfiner@ucsd.edu;
> >dale_phelps@urmc.rochester.edu; Tyson, Jon E; moshea@wfubmc.edu;
> >WOh@wihri.org; richard.ehrenkranz@yale.edu; higginsr@mail.nih.gov;
> >bkh@rti.org; poo@rti.org; Walid Salhab
> >Subject: Re: Updated COT Trial
> >
> >I think this is a very good idea
> >BJS"Abbot Laptook" <Abbot.Laptook@utsouthwestern.edu> writes:
> > >To all
> > > We have less concerns regarding the oxygenation arm since it
> > >should be transparent to the provider at the bedside, has safety
> > >features
> >built
> > >in, and it certainly has unique design features for studying
> >oxygenation
> > >as assessed by pulse oximetry. We do share all the concerns
> > >regarding the complexity of the ventilation arm and have offered a
> > >suggestion which may make it more feasible to get this study off
> > >the ground once all the details are worked out; ie consider
> > >initiaing the study in stages. The study could start with just the
> > >26-27 week strata for the first 4 months to identify problems that
> > >could not be anticipated and allow people in the units to deal with
> > >treatment guidelines for only 2 groups. Once we are on firm grounds
> > >with this strata, extend the study to the 24-25 wk infants and

> > >hopefully this will facilitate keeping all study requirements
> > >straight. AL
> > >
> > >>>> "William Oh" <WOh@wihri.org> 10/23/03 12:24:18 PM >>>
> > >Hi everyone: In a meeting today, I went over the protocol one more
> > >time with my faculty and fellows. There is a lot of concerns
> > >regarding the oxygenation arms of the protocol.The specific
> > >concerns include the high range of oxygen target (95%), nursing
> > >unable to use pulse oximeter for
> > >clinical monitoring, ust to name a few. While I support the study as I
> > >have indicated previously, I would appreciate the Committee's serious
> > >consideration for a trial that involves the CPAP arm only.
> > >
> > >Thanks
> > >
> > >
> > >Bill
> > >
> > >William Oh, MD
> > >Professor of Pediatrics
> > >Brown Medical School
> > >Attending Neonatologist
> > >Women and Infants' Hospital
> > >Providence RI 02905
> > >Phone (Office) 1 401 274 1122 ext.1432
> > > (Fax) 1 401 453 7571
> > >
> > >
> > >>>> "Seetha Shankaran M.D" <sshankar@med.wayne.edu> 10/23/03
> > >>>> 11:55AM
> > >>>>
> > >Hi all
> > >Yes, I had questioned the primary outcomes , need for separate arms
> > >of the study, and suggested sequential studies rather than
> > >factorial design. I do
> > >believe the COT committee has worked very hard at addressing issues
> > >raised.
> > >I support the study, knowing this will be a bear of a study to do. I
> > >believe the external reviews will be very helpful to us and look
> > >forward to
> > >seeing them. Sometimes we cannot see the forest for the trees.
> > >I have asked the committee to also study biochemical evidence of
> > >oxygen
> > >
> > >toxicity (such as Vento's work on reduced to oxidized glutathione
> > >ratios in term infants resuscitated with 100% oxygen). These
> > >discussions are very useful Thanks for sharing
> > >Seetha
> > >
> > >
> > >
> > > At 04:18 PM 10/22/03 -0400, Edward Donovan wrote:
> > >>Yes, but.
> > >>We did enroll "under duress" in the pilot with some success. The
> > >>SAVE trial was factorial and I think the consent rate and
> > >enrollment
> > >>rate were similar to our other simpler trials.
> > >>We are told that we are funded to do the trials that cannot be
> > >>done
> > >by

> > >
> > >>less sophisticated groups.
> > >>This is a difficult and expensive trial, I agree. But, with the
> > >>resources, we should be able to do it. 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
> > >><http://www.cprc-chmc.uc.edu>www.cprc-chmc.uc.edu
> > >>
> > >> >>> "Lemons, James A" <jlemons@iupui.edu> 10/20/2003 5:29:03 PM
> > >> >>> >>>
> > >>We still believe this is going to be an extremely difficult trial
> > >>to implement and complete. This is due to the complexity of
> > >>incorporating
> > >>two separate trials with two separate primary outcomes into a
> > >>singe factorial designed studey (for which the rationale is still
> > >>unclear),
> > >>as
> > >>well as the short window for consenting. As challenging as
> > >>enrollment
> > >>has
> > >>been for phototherapy because of the narrower window, enrollment
> > >>for
> > >>this
> > >>trial will be extraordinarily challenging as the window is even
> > >>tighter. And explaining this complex trial with two separate
> > >>studies
> > >>to
> > >>parents under duress will require that much more time. This will
> > >>be compounded for large centers with multiple sites and many more
> > >>people
> > >>
> > >>involved. While we will attempt to support this trial if approved
> > >>by
> > >>the
> > >>Steering Committe and outside reviewers, the logistical challenges
> > >>of
> > >>
> > >>implementing and enrolling at reasonable rates we perceive as
> > >>extremely
> > >>difficult.
> > >> Thanks, Jim -----Original
> > >>Message-----
> > >>From: Petrie, Carolyn [mailto:petrie@rti.org]
> > >>Sent: Friday, October 17, 2003 1:27 PM
> > >>To: 'M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu)'; 'M.
> > >>D.
> > >>Alan
> > >>Jobe (Jobea0@chmcc.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)';
> > >>Lemons, James A; '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)';
> > >
> > >>'Seetha Shankaran (sshankar@med.wayne.edu)'; 'William Oh2
> > >(WOh@wihri.org)'
> > >>Cc: 'aRose Higgins (higginsr@mail.nih.gov)'; Hastings, Betty J.;
> > >Petrie,
> > >>Carolyn; Poole, W. Kenneth
> > >>Subject: RE: Updated COT Trial
> > >>
> > >>Reminder that today is the deadline for your comments:
> > >>To the Neonatal Research Network Steering Committee: Attached is
> > >>the latest COT trial for your input. Please send
> > >comments
> > >by
> > >>Friday, October 17.
> > >>Thanks!
> > >>Carolyn
> > >>
> > >
> > >
> > >
> > >Seetha Shankaran, MD
> > >Professor of Pediatrics
> > >Director, Neonatal-Perinatal Medicine
> > >Wayne State University School of Medicine
> > >(313) 745-1436
> > >sshankar@med.wayne.edu
>
> _____
> Richard A. Ehrenkranz, MD
> Department of Pediatrics
> Yale University School of Medicine
> 333 Cedar Street
> PO Box 208064
> New Haven, CT 06520-8064
> tele: 203-688-2320
> fax: 203-688-5426
>
> The information contained in this email may be privileged and
confidential.
> If you are the intended recipient, you must maintain this message in a
> secure and confidential manner. If you are not the intended
> recipient, please notify the sender immediately and destroy this
> message. Thank you.

From:	Neil Finer
To:	Carmen M Hererra
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: COT trial
Date:	Friday, October 24, 2003 10:53:32 AM

Hi Carmen
Thanks for your input. I will add hemodynamic stability as a criteria - I would indicate that hemodynamic stability is a stable blood pressure for age, with evidence of adequate perfusion in the absence of the need for pressor or volume support. Do you think that this is acceptable?
The more we have tried to standardize the more groups object that they don't do things that way. We have chosen (for better or worse) to try to be less prescriptive for the Control infants, and force the Treatment infants to extubation.
Nasal SIMV is an option and can be used in any infant. The Star is going away. We are trying to develop a sensor that would work with any vent. That is not close at present. We would not be able to supply any device to all centers for this, and few Network centers use SIMV. I have looked at this, and besides ourselves, Yale, and Alabama were frequent users with Rochester using some. Duke had been noted to use for only 3 infants for data from the previous year.
We have decided not to further complicate issues by trying to introduce this to sites who don't use it, ie Most sites.
Your comments are most helpful. I have a question for you - Does your site have any enthusiasm for this trial??
Thanks
Be well
Neil

----- Original Message -----
From: "Carmen M Hererra" <herre004@mc.duke.edu>
To: <nfiner@ucsd.edu>
Cc: "Ronald N Goldberg" <goldb008@mc.duke.edu>
Sent: Thursday, October 23, 2003 4:23 PM
Subject: COT trial

>
>
>
>
>
> Dear Neil,
>
> Ron is out of the country and he asked me to make sure you were aware of
> our main concerns regarding this important trial.
>
> 1. Extubation criteria for infants 24-25 weeks: Our group does not feel
> comfortable extubating infants who are hemodynamically unstable even if
> they meet these criteria. We know that ELBW babies have a high extubation
> failure rate (at least 40%) and that infants who need to be reintubated
> usually require higher settings than prior to extubation. This figure
> includes mostly infants who were deemed ready for extubation and it is
> reasonable to expect it would be even higher in hemodynamically unstable
> patients. Therefore, we believe parameters of hemodynamical stability (ie.
> no vasopressor requirement, absence of hemodynamically significant PDA,

> etc) should be included in the extubation parameters.
>
> 2. There is no standardization of the control arm ("permissive ventilatory
> strategy"). It reminds me of the earlier HFV versus conventional
> ventilation trials were no definitive conclusions could be drawn because
> the conventional intervention (control) was highly variable and not
> optimized.
>
> 3. Nasal SIMV: We used to have InfantStar ventilators to deliver nasal
> SIMV, but they are not manufactured anymore and it is difficult to get them
> repaired. What devices are other centers using? Ideally this modality
> should be available to all centers as it has shown to have advantages over
> conventional CPAP.
>
> Please let me know if you have any questions about any of the above.
>
> Carmen Herrera
> Duke
>

From: Wally Carlo, M.D.
To: "Lemons, James A"; Neil Finer
Cc: Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Updated COT Trial
Date: Thursday, October 23, 2003 12:01:18 PM

Jim: That is a good point and we thought carefully about it. That will be the primary hypothesis of the ventilation arm and a secondary hypothesis for the combination of the interventions. Wally

-----Original Message-----
From: Lemons, James A [mailto:jlemons@iupui.edu]
Sent: Thursday, October 23, 2003 10:55 AM
To: Wally Carlo, M.D.; Neil Finer
Cc: Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Updated COT Trial

I agree - then why is our study not designed and powered around a single primary outcome of survival without CLD, rather that CLD and ROP?

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@PEDS.UAB.EDU]
Sent: Thursday, October 23, 2003 10:46 AM
To: Lemons, James A; Neil Finer
Cc: Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Updated COT Trial

Jim: Precisely, there are two RCTs (Stop-ROP and BOOST) using different a design of ranges in saturation (late intervention to two O2 sat ranges) which showed that BPD is increased by aiming for higher sats. However, those studies evaluated the therapy in more mature infants who already had lung injury. The COT trial will be innovative as it may dissect the contributions of a ventilation and an oxygenation intervention. A trial to only test the O2 question is also being designed outide of the Network but the timetable for completion is around the year 2010 as it will be a very large trial to even detect very small effects. Wally

-----Original Message-----
From: Lemons, James A [mailto:jlemons@iupui.edu]
Sent: Thursday, October 23, 2003 10:35 AM
To: Neil Finer
Cc: Wally Carlo, M.D.; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: Updated COT Trial

Neal,
I appreciate your thoughtful comments - and I know we have discussed this before. Factorial design is for independent arms which share a primary outcome (such as the SAVE Trial). If there are data to indicate that O2 sats affect the incidence of CLD, then factorial design would be appropriate for a shared primary outcome. I simply worry that we may be compromising our ability to successfully enroll patients by having to explain two independent studies in a time of crisis for the parents. While both of these studies are of interest, I just want us to have the best chance of succeeding in the most important study arm (at least it was as you first developed this protocol) - the DR CPAP issue. We will certainly support the trial at Indiana, however it finally emerges. Thanks, Jim

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, October 22, 2003 7:45 PM

To: Lemons, James A
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: Updated COT Trial

Hello Jim
I have followed the correspondence generated by your thoughts.
This is a somewhat complex trial. All factorial designs attempt to answer more than a single question. We believe that these 2 maneuvers may be additive in producing better outcomes, and that both of the planned interventions are relevant to current practice. Doing each separately will take twice as long, and will not educate us as to whether a permissive strategy with a lower target SpO2 is a better overall approach (or any other combination).
The factorial really replaces random clinical variation with prospective randomization as all units now use a range of SpO2, usually undefined, and not similar to the other centers. This represents noise currently when we try to analyze results.
We often present parents with more than one study during our prenatal visits, and for this trial they only have to read and understand a single consent.
We have tried to simplify the ventilation interventions as much as we can and made initial DR management for the 24-25 weekers identical. The study differences start at 1 hour with an approach to extubation if criteria are met. This is a group that no one has studied or is currently attempting to study, and has the highest morbidity.
For the larger infants, we are allowing the sites to follow current practice to use early or prophylactic surfactant for the control infants and CPAP for the treatment infants. We have tried to keep the criteria for intubation and extubation relatively simple, and close to what is current overall for the control infants. No one has attempted to compare CPAP with DR or early surfactant, and VON will have that in their 3 arm trial. We think that this larger group of 26 - 27 weeks is ideal to make this comparison.
The SpO2 arm will be transparent to the caretakers and thus really doesn't add clinical complexity. There is more work for research personnel to get the downloads and encourage monitoring of the SpO2 ranges, but the study pulse oximeters will become the infants bedside oximeter, and he/she will be monitored as is current with a different target range. I'm not even concerned that we have a tight target range and believe that 85% to 95% will be fine and demonstrate a difference in the actual achieved SpO2 ranges.
We have avoided stringent weaning criteria, allowed for local practice in the management of Control infants in that extubation can be done when criteria are met but extubation may be delayed if that is more in keeping with current practice. The problem will be the willingness of the teams to wait for criteria to intubate the treatment infants, and extubate the treatment infants when they meet criteria. I expect significant failures in the 24-25 week infants, and we are allowing a period of up to 48 hours before a re-extubation need be done.
Jim as Av indicated, this is a challenging but potentially very informative trial.
If we are to successfully complete this trial there will have to be enthusiastic participation from a majority of sites.
We are awaiting a final decision, and I hope that your group will be involved.
Regards
Neil

----- Original Message -----
From: Lemons, James A
To: Petrie, Carolyn ; abbot.laptook@utsouthwestern.edu ; Jobea0@chmcc.org ; aaf2@cwru.edu ; barbara_stoll@oz.ped.emory.edu ; dale_phelps@urmc.rochester.edu ; dstevenson@stanford.edu ; edward.donovan@chmcc.org ; jon.e.tyson@uth.tmc.edu ; moshea@wfubmc.edu ; nfiner@ucsd.edu ; richard.ehrenkranz@yale.edu ; goldb008@mc.duke.edu ; sduara@miami.edu ; wcarlo@peds.uab.edu ; sshankar@med.wayne.edu ; WOh@wihri.org
Cc: higginsr@mail.nih.gov ; Hastings, Betty J. ; Poole, W. Kenneth
Sent: Monday, October 20, 2003 2:29 PM
Subject: RE: Updated COT Trial

We still believe this is going to be an extremely difficult trial to implement and complete. This is due to the complexity of incorporating two separate trials with two separate primary outcomes into a singe factorial designed studey (for which the rationale is still unclear), as well as the short window for consenting. As challenging as enrollment has been for phototherapy because of the narrower window, enrollment for this trial will be extraordinarily challenging as the window is even tighter. And explaining this complex trial with two separate studies to parents under duress will require that much more time. This will be compounded for large centers with multiple sites and many more people involved. While we will attempt to support this trial if approved by the Steering Committe and outside reviewers, the logistical challenges of implementing and enrolling at reasonable rates we perceive as extremely difficult.

Thanks, Jim

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, October 17, 2003 1:27 PM
To: 'M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu)'; 'M. D. Alan Jobe (Jobea0@chmcc.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)'; Lemons, James A; '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)'; 'Seetha Shankaran (sshankar@med.wayne.edu)'; 'William Oh2 (WOh@wihri.org)'
Cc: 'aRose Higgins (higginsr@mail.nih.gov)'; Hastings, Betty J.; Petrie, Carolyn; Poole, W. Kenneth
Subject: RE: Updated COT Trial

Reminder that today is the deadline for your comments:

To the Neonatal Research Network Steering Committee:

Attached is the latest COT trial for your input. Please send comments by **Friday, October 17**.

Thanks!

Carolyn

From: Avroy A. Fanaroff
To: Shahnaz Duara; "Neil Finer"; "Lemons, James A"
Cc: "Wally Carlo, M.D."; Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff, M.D."; "Ed Donovan"
Subject: RE: Updated COT Trial
Date: Thursday, October 23, 2003 9:35:35 AM

Agree
Av
At 09:13 AM 10/23/2003 -0400, Shahnaz Duara wrote:

> Great response
> Shahnaz
>
> > -----Original Message-----
> > From: Neil Finer [mailto:nfiner@ucsd.edu]
> > Sent: Wednesday, October 22, 2003 8:45 PM
> > To: Lemons, James A
> > Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
> > Subject: Re: Updated COT Trial
> >
> > Hello Jim
> > I have followed the correspondence generated by your thoughts.
> > This is a somewhat complex trial. All factorial designs attempt to answer more than a single question. We believe that these 2 maneuvers may be additive in producing better outcomes, and that both of the planned interventions are relevant to current practice. Doing each separately will take twice as long, and will not educate us as to whether a permissive strategy with a lower target SpO2 is a better overall approach (or any other combination).
> > The factorial really replaces random clinical variation with prospective randomization as all units now use a range of SpO2, usually undefined, and not similar to the other centers. This represents noise currently when we try to analyze results.
> > We often present parents with more than one study during our prenatal visits, and for this trial they only have to read and understand a single consent.
> > We have tried to simplify the ventilation interventions as much as we can and made initial DR management for the 24-25 weekers identical. The study differences start at 1 hour with an approach to extubation if criteria are met. This is a group that no one has studied or is currently attempting to study, and has the highest morbidity.
> > For the larger infants, we are allowing the sites to follow current practice to use early or prophylactic surfactant for the control infants and CPAP for the treatment infants. We have tried to keep the criteria for intubation and extubation relatively simple, and close to what is current overall for the control infants. No one has attempted to compare CPAP with DR or early surfactant, and VON will have that in their 3 arm trial. We think that this larger group of 26 - 27 weeks is ideal to make this comparison.
> > The SpO2 arm will be transparent to the caretakers and thus really doesn't add clinical complexity. There is more work for research personnel to get the downloads and encourage monitoring of the SpO2 ranges, but the study pulse oximeters will become the infants bedside oximeter, and he/she will be monitored as is current with a different target range. I'm not even concerned that we have a tight target range and believe that 85% to 95% will be fine and demonstrate a difference in the actual achieved SpO2 ranges.
> > We have avoided stringent weaning criteria, allowed for local practice in the management of Control infants in that extubation can be done when criteria are

met but extubation may be delayed if that is more in keeping with current practice. The problem will be the willingness of the teams to wait for criteria to intubate the treatment infants, and extubate the treatment infants when they meet criteria. I expect significant failures in the 24-25 week infants, and we are allowing a period of up to 48 hours before a re-extubation need be done.
Jim as Av indicated, this is a challenging but potentially very informative trial. If we are to successfully complete this trial there will have to be enthusiastic participation from a majority of sites.
We are awaiting a final decision, and I hope that your group will be involved.
Regards
Neil

----- Original Message -----
From: Lemons, James A
To: Petrie, Carolyn ; abbot.laptook@utsouthwestern.edu ; Jobea0@chmcc.org ; aaf2@cwru.edu ; barbara_stoll@oz.ped.emory.edu ; dale_phelps@urmc.rochester.edu ; dstevenson@stanford.edu ; edward.donovan@chmcc.org ; jon.e.tyson@uth.tmc.edu ; moshea@wfubmc.edu ; nfiner@ucsd.edu ; richard.ehrenkranz@yale.edu ; goldb008@mc.duke.edu ; sduara@miami.edu ; wcarlo@peds.uab.edu ; sshankar@med.wayne.edu ; WOh@wihri.org
Cc: higginsr@mail.nih.gov ; Hastings, Betty J. ; Poole, W. Kenneth
Sent: Monday, October 20, 2003 2:29 PM
Subject: RE: Updated COT Trial

We still believe this is going to be an extremely difficult trial to implement and complete. This is due to the complexity of incorporating two separate trials with two separate primary outcomes into a singe factorial designed studey (for which the rationale is still unclear), as well as the short window for consenting. As challenging as enrollment has been for phototherapy because of the narrower window, enrollment for this trial will be extraordinarily challenging as the window is even tighter. And explaining this complex trial with two separate studies to parents under duress will require that much more time. This will be compounded for large centers with multiple sites and many more people involved. While we will attempt to support this trial if approved by the Steering Committe and outside reviewers, the logistical challenges of implementing and enrolling at reasonable rates we perceive as extremely difficult.

Thanks, Jim

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, October 17, 2003 1:27 PM
To: 'M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu)'; 'M. D. Alan Jobe (Jobea0@chmcc.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)'; Lemons, James A; '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)'; 'Seetha Shankaran (sshankar@med.wayne.edu)'; 'William Oh2 (WOh@wihri.org)'
Cc: 'aRose Higgins (higginsr@mail.nih.gov)'; Hastings, Betty J.; Petrie, Carolyn; Poole, W. Kenneth
Subject: RE: Updated COT Trial

Reminder that today is the deadline for your comments:

To the Neonatal Research Network Steering Committee:
Attached is the latest COT trial for your input. Please send comments by Friday, October 17.
Thanks!
Carolyn

From: Avroy A. Fanaroff
To: Shahnaz Duara; "Neil Finer"; "Edward Donovan"; aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); WCarlo@PEDS.UAB.EDU; aaf2@cwru.edu
Subject: RE: COT Trial comments
Date: Wednesday, October 22, 2003 10:12:36 PM

Hi
I am at a conference in Michigan and will not be available either day. Apologies
Av
At 08:02 PM 10/22/2003 -0400, Shahnaz Duara wrote:

> Either afternoon is OK with me, but please don't do the 'low bid' arrangements again (just kidding!)
> Shahnaz
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, October 22, 2003 4:35 PM
> To: Edward Donovan; aaf2@cwru.edu; higginsr@mail.nih.gov; sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu
> Subject: Re: COT Trial comments
>
> Are you all available for a Conference Call tomorrow or Friday say around 12:00 PT or 3:00 Eastern Time?
> Please let me know and I can do it from here.
> Many thanks
> Neil
> ----- Original Message -----
> From: Edward Donovan
> To: aaf2@cwru.edu ; higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
> Sent: Wednesday, October 22, 2003 1:12 PM
> Subject: Re: COT Trial comments
>
> One problem with requiring "a lot" of blood gases is that clinicians and parents will view the study as "invasive" and this might inhibit enrollment. It seems to me that gases tend to be "one point in time" events that may or may not reflect overall well being of the infant. If there is no indwelling arterial catheter, I believe that the stick itself significantly alters gas exchange. Also, if the intervention only works with frequent blood gases, then it may be difficult to disseminate to the real world.
> 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> 10/17/2003 11:54:49 PM
> >>>

Hi
I have been on service and trying to avoid my email.
Well, success has a strange definition, we have pleased those that squeaked
the loudest, and developed a protocol that may be acceptable to the Network
while having sacrificed some major defining differences between the groups.
I would suggest that if we get the go ahead, we develop the study manual to
include mandatory blood gases at least q 6 - 8 h for the first 48 hours, and
force the extubation of the Treatment small infants by enforcing the current
protocol - There is little squeak room here, they will all have study Pulse
oximeters by 1 hour and we will do a data dump at 72 hours, thus we will
have the SpO2 at 1 hour. We have a data sheet that includes the actual FiO2
at 1 hour and a 1 hr blood gas.
In addition we follow Wally's suggestions regarding study monitoring. We can
make a number of changes to the actual details and strengthen the differences. Please think about how to tighten this up. Once approved, the
manual will be the protocol!!
We never mentioned blood gases as yet, that is not to say we are not going
to insist on them.
We have allowed the use of Nasal SIMV, we also are advocates of that
approach. I believe that the current protocol for the larger strata will be
different as we have forced intubation of the Control infants for surfactant
by 1 hr and not for the Treatment infants. Most centers do not do rapid
extubation, and I doubt that they will now change. We would ask each site to
file its current approach before the trial. Please give all this some thought.
Me. I am waiting to hear that we have been approved to move ahead. I
indicated to Cynthia Cole that we were almost there and Massimo is moving
ahead.
Wally. Masimo will have POs available within 4 - 6 weeks after we finalize
the ranges. Cynthia seems to like our current limits as did Bill Hay. I will
try to finalize.
Thanks for staying tuned.

Neil
----- Original Message -----
From: "Shahnaz Duara" <sduara@miami.edu>
To: "'Avroy A. Fanaroff'" <aaf2@po.cwru.edu>; "'Wally Carlo, M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Neil Finer'" <nfiner@ucsd.edu>; <higginsr@mail.nih.gov>; "'Avroy A. Fanaroff, M.D.'" <aaf2@cwru.edu>; "'Ed Donovan'" <Edward.Donovan@chmcc.org>
Sent: Friday, October 17, 2003 9:03 AM
Subject: RE: COT Trial comments

Dear All,

I agree with much of what Richard has to say. Unfortunately for the trial, we have struck a compromise situation which fits the 'comfort zone' of the many neonatologists who need to comply with the study. It doesn't hurt to have the Yale group and Abbott's group go on record as wanting more mandates to separate the study groups. If similar requests come in greater numbers, we have an opportunity to say that by 'popular request' we are adding some mandates. Will that fly with the majority?

Miami certainly feels that there should be more prescribing of what is allowed to happen subsequently to treatment group infants who remain intubated (appropriately) at 24 +/-2 hours - as the protocol stands, there is no given interval as to how often subsequent blood gases are to be done, and there is no weaning strategy. Centers who prefer to leave a baby intubated can spread out gas sampling, in addition to manipulating the vent settings, as Richard points out. This would certainly drift the two arms together, particularly for the smaller infants - the take home message would then be that CPAP as a primary treatment modality is untestable in the 24-25 week GA group prospectively.

We support and are able to do the trial as it stands, but feel it could be strengthened if it were tightened, so long as there was group agreement for the importance of the additions and willingness to comply.

The world could never have been created in seven days if academic neonatologists had been involved.

Shahnaz

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Friday, October 17, 2003 9:59 AM
To: Wally Carlo, M.D.; 'Neil Finer'; Shahnaz Duara; higginsr@mail.nih.gov;
Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial comments

Hi
Good points made by Richard, but we have been through most of them before It
is becoming apparent again how difficult it is to design an intervention
trial - and given the current outcomes to be able to show a difference
between two treatment arms.
As I reflect on this more and more I think that we have massaged the study
design to the max and will be going around in circles if we start modifying
it again.
The main strength of the trial may be the saturation groups - this still
makes for a compelling trial.
Av
At 06:50 AM 10/17/2003, Wally Carlo, M.D. wrote:
>The solution is to have different CO2/pH targets before extubation as
>we have previously discussed. wally
>
>-----Original Message-----
>From: Neil Finer [mailto:nfiner@ucsd.edu]
>Sent: Thursday, October 16, 2003 7:22 PM
>To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer;
>higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
>Subject: Fw: COT Trial comments
>
>
>
>----- Original Message -----
>From: "Richard A Ehrenkranz" <richard.ehrenkranz@yale.edu>
>To: <nfiner@ucsd.edu>
>Sent: Thursday, October 16, 2003 2:50 PM
>Subject: Fwd: COT Trial comments
>
>

> > Neil:
> >
> > I am sorry if you got this email already, but it seemed to bounce
> > back.
> >
> > Richard
> >
> >
> > >Date: Thu, 16 Oct 2003 17:18:08 -0400
> > >To: Neil N Finer
> > >From: Richard A Ehrenkranz <richard.ehrenkranz@yale.edu>
> > >Subject: COT Trial comments
> > >Cc: Rosemary Higgins, Carolyn Petrie
> > >
> > >Neil:
> > >
> > >Members of my Division have reviewed the revised COT trial and I
> > >have had an opportunity to speak to most of them individually or in
> > >small groups. I have also received some written comments. I will
> > >summarize these comments:
> > >
> > >Our group is willing to participate in a RCT that seeks to evaluate
> > >a strategy that will increase survival without BPD at 36 weeks PMA.
> > >We are willing to change our current practice and administer
> > >surfactant in the
>DR
> > >and/or within 30 minutes of birth. However, we are concerned that
> > >the design of the current protocol will not demonstrate any
> > >difference
>between
> > >the study groups because we believe that, in clinical practice,
> > >there
>will
> > >be minimal difference between the proposed management plans. The
> > >major difference between the study groups for the 24-25 week strata
> > >is the forced extubation at less than 1 hour if a treatment arm
> > >infant meets extubation criteria; the re-intubation criteria are
> > >not that different. Since centers are to employ their usual
> > >resuscitation equipment for control infants in the 26-27 week
> > >strata, the management of control infants in centers (like ours)
> > >that use ventilators in the DR to provide PPV (with CPAP) may not

> > >be very different than the management of infants in the treatment
> > >arm. Even accepting the difference between the meaning of "may" vs
> > >"must," the criteria for intubation for surfactant, extubation, and
> > >re-intubation are not that different, making us wonder about the
> > >potential for manipulating FiO2 and ventilator settings to comply
> > >with the preference of the team rather than the protocol.
> > >Therefore, we question whether the study design will elicit >any
> > >difference between these two treatment arms. In an effort to
> > >achieve clear differences between the study groups, we previously
> > >suggested that all control infants should be intubated in the DR,
> > >receive surfactant promptly and not be eligible for a forced
> > >extubation to CPAP or NSIMV.
> > >
> > >We are concurrently performing a trial in which intubated infants
> > >between 600-1250 g birth weight are given early surfactant and then
> > >randomized to NSIMV vs continued PPV. Our limited experience with
> > >the smallest infants makes us somewhat nervous about the forced
> > >extubation in the 24-25 weeks treatment arm strata. Almost all of
> > >the smallest infants have required re-intubation and prolonged
> > >ventilatory courses. We started this trial after Vineet Bhandari
> > >joined the group. He is a strong advocate of NSIMV and we had
> > >hoped it would give us some data to support it's use in this trial
> > >(which was already being discussed).
> > >
> > >We continue to have no difficulty with the SpO2 intervention.
> > >
> > >In summary, we would like to participate in this trial, but would
> > >like to feel that there is a distinct difference between the study
> > >arms.
> > >
> > >Richard
> > >
> > >

> > >
> > >_____
> > >Richard A. Ehrenkranz, MD
> > >Department of Pediatrics
> > >Yale University School of Medicine
> > >333 Cedar Street
> > >PO Box 208064
> > >New Haven, CT 06520-8064
> > >tele: 203-688-2320
> > >fax: 203-688-5426
> > >
> > >The information contained in this email may be privileged
and
>confidential.
> > >If you are the intended recipient, you must maintain this
message
> > >in a
>secure
> > >and confidential manner. If you are not the intended
recipient,
> > >please notify the sender immediately and destroy this
message.
> > >Thank you.
> >
> > _____
> > Richard A. Ehrenkranz, MD
> > Department of Pediatrics
> > Yale University School of Medicine
> > 333 Cedar Street
> > PO Box 208064
> > New Haven, CT 06520-8064
> > tele: 203-688-2320
> > fax: 203-688-5426
> >
> > The information contained in this email may be privileged and
>confidential.
> > If you are the intended recipient, you must maintain this
message in
> > a
>secure
> > and confidential manner. If you are not the intended recipient,
> > please
>notify
> > the sender immediately and destroy this message. Thank you.
> >

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884

Fax 216-844-1479

The enclosed information is STRICTLY CONFIDENTIAL and is intended for the use of the addressee only. University Hospitals Health System and its affiliates disclaim any responsibility for unauthorized disclosure of this information to anyone other than the addressee.

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Wally Carlo, M.D.
To: "Edward Donovan"; aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: COT Trial comments
Date: Wednesday, October 22, 2003 4:51:47 PM

I agree. These kids are sick enough that they already get too many blood gases. What we need is to act on them. I suggest a coordinator checks twice a day (early AM and late PM) to make sure the protocol is being followed. If it is not, suggestions to the clinicians would usually make them compliant with the protocol. Rarely would intervention by the PI/opinion leader would be necessary. Blood gas data could be collected at a designated time (eg 12 noon) plus or minus 12 hours if available during the acute phase. Wally

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Wednesday, October 22, 2003 3:13 PM
To: aaf2@cwru.edu; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: Re: COT Trial comments

One problem with requiring "a lot" of blood gases is that clinicians and parents will view the study as "invasive" and this might inhibit enrollment. It seems to me that gases tend to be "one point in time" events that may or may not reflect overall well being of the infant. If there is no indwelling arterial catheter, I believe that the stick itself significantly alters gas exchange. Also, if the intervention only works with frequent blood gases, then it may be difficult to disseminate to the real world.

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> 10/17/2003 11:54:49 PM >>>
Hi
I have been on service and trying to avoid my email.
Well, success has a strange definition, we have pleased those that squeaked the loudest, and developed a protocol that may be acceptable to the Network while having sacrificed some major defining differences between the groups.
I would suggest that if we get the go ahead, we develop the study manual to include mandatory blood gases at least q 6 - 8 h for the first 48 hours, and force the extubation of the Treatment small infants by enforcing the current protocol - There is little squeak room here, they will all have study Pulse oximeters by 1 hour and we will do a data dump at 72 hours, thus we will have the SpO2 at 1 hour. We have a data sheet that includes the actual FiO2 at 1 hour and a 1 hr blood gas.
In addition we follow Wally's suggestions regarding study monitoring. We can make a number of changes to the actual details and strengthen the differences. Please think about how to tighten this up. Once approved, the manual will be the protocol!!
We never mentioned blood gases as yet, that is not to say we are not going to insist on them.
We have allowed the use of Nasal SIMV, we also are advocates of that approach. I believe that the current protocol for the larger strata will be

different as we have forced intubation of the Control infants for surfactant by 1 hr and not for the Treatment infants. Most centers do not do rapid extubation, and I doubt that they will now change. We would ask each site to file its current approach before the trial. Please give all this some thought.
Me. I am waiting to hear that we have been approved to move ahead. I indicated to Cynthia Cole that we were almost there and Massimo is moving ahead.
Wally. Masimo will have POs available within 4 - 6 weeks after we finalize the ranges. Cynthia seems to like our current limits as did Bill Hay. I will try to finalize.
Thanks for staying tuned.
Neil
----- Original Message -----
From: "Shahnaz Duara" <sduara@miami.edu>
To: "'Avroy A. Fanaroff" <aaf2@po.cwru.edu>; "'Wally Carlo, M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Neil Finer'" <nfiner@ucsd.edu>; <higginsr@mail.nih.gov>; "'Avroy A. Fanaroff, M.D.'" <aaf2@cwru.edu>; "'Ed Donovan'" <Edward.Donovan@chmcc.org>
Sent: Friday, October 17, 2003 9:03 AM
Subject: RE: COT Trial comments

Dear All,

I agree with much of what Richard has to say. Unfortunately for the trial, we have struck a compromise situation which fits the 'comfort zone' of the many neonatologists who need to comply with the study. It doesn't hurt to have the Yale group and Abbott's group go on record as wanting more mandates to separate the study groups. If similar requests come in greater numbers, we have an opportunity to say that by 'popular request' we are adding some mandates. Will that fly with the majority?

Miami certainly feels that there should be more prescribing of what is allowed to happen subsequently to treatment group infants who remain intubated (appropriately) at 24 +/-2 hours - as the protocol stands, there is no given interval as to how often subsequent blood gases are to be done, and there is no weaning strategy. Centers who prefer to leave a baby intubated can spread out gas sampling, in addition to manipulating the vent settings, as Richard points out. This would certainly drift the two arms together, particularly for the smaller infants - the take home message would then be that CPAP as a primary treatment modality is untestable in the 24-25 week GA group prospectively.

We support and are able to do the trial as it stands, but feel it could be strengthened if it were tightened, so long as there was group agreement for the importance of the additions and willingness to comply.

The world could never have been created in seven days if academic neonatologists had been involved.

Shahnaz

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Friday, October 17, 2003 9:59 AM
To: Wally Carlo, M.D.; 'Neil Finer'; Shahnaz Duara; higginsr@mail.nih.gov;

Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial comments

Hi
Good points made by Richard, but we have been through most of them before It is becoming apparent again how difficult it is to design an intervention trial - and given the current outcomes to be able to show a difference between two treatment arms.
As I reflect on this more and more I think that we have massaged the study design to the max and will be going around in circles if we start modifying it again.
The main strength of the trial may be the saturation groups - this still makes for a compelling trial.
Av
At 06:50 AM 10/17/2003, Wally Carlo, M.D. wrote:
>The solution is to have different CO2/pH targets before extubation as
>we have previously discussed. wally
>
>-----Original Message-----
>From: Neil Finer [mailto:nfiner@ucsd.edu]
>Sent: Thursday, October 16, 2003 7:22 PM
>To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer;
>higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
>Subject: Fw: COT Trial comments
>
>
>
>----- Original Message -----
>From: "Richard A Ehrenkranz" <richard.ehrenkranz@yale.edu>
>To: <nfiner@ucsd.edu>
>Sent: Thursday, October 16, 2003 2:50 PM
>Subject: Fwd: COT Trial comments
>
>
> > Neil:
> >
> > I am sorry if you got this email already, but it seemed to bounce
> > back.
> >
> > Richard
> >
> >
> > >Date: Thu, 16 Oct 2003 17:18:08 -0400
> > >To: Neil N Finer
> > >From: Richard A Ehrenkranz <richard.ehrenkranz@yale.edu>
> > >Subject: COT Trial comments
> > >Cc: Rosemary Higgins, Carolyn Petrie
> > >
> > >Neil:
> > >
> > >Members of my Division have reviewed the revised COT trial and I
> > >have had an opportunity to speak to most of them individually or in
> > >small groups. I have also received some written comments. I will
> > >summarize these comments:
> > >
> > >Our group is willing to participate in a RCT that seeks to evaluate

> > >a strategy that will increase survival without BPD at 36 weeks PMA.
> > >We are willing to change our current practice and administer
> > >surfactant in the
>DR
> > >and/or within 30 minutes of birth. However, we are concerned that
> > >the design of the current protocol will not demonstrate any
> > >difference
>between
> > >the study groups because we believe that, in clinical practice,
> > >there
>will
> > >be minimal difference between the proposed management plans. The
> > >major difference between the study groups for the 24-25 week strata
> > >is the forced extubation at less than 1 hour if a treatment arm
> > >infant meets extubation criteria; the re-intubation criteria are
> > >not that different. Since centers are to employ their usual
> > >resuscitation equipment for control infants in the 26-27 week
> > >strata, the management of control infants in centers (like ours)
> > >that use ventilators in the DR to provide PPV (with CPAP) may not
> > >be very different than the management of infants in the treatment
> > >arm. Even accepting the difference between the meaning of "may" vs
> > >"must," the criteria for intubation for surfactant, extubation, and
> > >re-intubation are not that different, making us wonder about the
> > >potential for manipulating FiO2 and ventilator settings to comply
> > >with the preference of the team rather than the protocol.
> > >Therefore, we question whether the study design will elicit
>any
> > >difference between these two treatment arms. In an effort to
> > >achieve clear differences between the study groups, we previously
> > >suggested that all control infants should be intubated in the DR,
> > >receive surfactant promptly and not be eligible for a forced
> > >extubation to CPAP or NSIMV.
> > >
> > >We are concurrently performing a trial in which intubated infants
> > >between 600-1250 g birth weight are given early surfactant and then
> > >randomized to NSIMV vs continued PPV. Our limited experience with
> > >the smallest infants makes us somewhat nervous about the forced
> > >extubation in the 24-25 weeks treatment arm strata. Almost all of
> > >the smallest infants have required re-intubation and prolonged
> > >ventilatory courses. We started this trial after Vineet Bhandari
> > >joined the group. He is a strong advocate of NSIMV and we had
> > >hoped it would give us some data to support it's use in this trial
> > >(which was already being discussed).
> > >
> > >We continue to have no difficulty with the SpO2 intervention.
> > >
> > >In summary, we would like to participate in this trial, but would
> > >like to feel that there is a distinct difference between the study
> > >arms.
> > >
> > >Richard
> > >
> > >
> > >
> > >_____
> > >Richard A. Ehrenkranz, MD
> > >Department of Pediatrics

> > >Yale University School of Medicine
> > >333 Cedar Street
> > >PO Box 208064
> > >New Haven, CT 06520-8064
> > >tele: 203-688-2320
> > >fax: 203-688-5426
> > >
> > >The information contained in this email may be privileged and
>confidential.
> > >If you are the intended recipient, you must maintain this message
> > >in a
>secure
> > >and confidential manner. If you are not the intended recipient,
> > >please notify the sender immediately and destroy this message.
> > >Thank you.
> >
> > _____
> > Richard A. Ehrenkranz, MD
> > Department of Pediatrics
> > Yale University School of Medicine
> > 333 Cedar Street
> > PO Box 208064
> > New Haven, CT 06520-8064
> > tele: 203-688-2320
> > fax: 203-688-5426
> >
> > The information contained in this email may be privileged and
>confidential.
> > If you are the intended recipient, you must maintain this message in
> > a
>secure
> > and confidential manner. If you are not the intended recipient,
> > please
>notify
> > the sender immediately and destroy this message. Thank you.
> >

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884
Fax 216-844-1479

CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Wally Carlo, M.D.
To: "Neil Finer"
Cc: Higgins, Rosemary (NIH/NICHD); "Petrie, Carolyn"
Subject: RE: COT Trial comments
Date: Wednesday, October 22, 2003 4:46:10 PM

Neil: I can do it Thursday at that time and almost any other time except up to 10 AM eastern (this one I can not change). On Friday, I have to be DONE by 3 pm Eastern but any other time would be ok (I will rearrange my schedule). You do not have to check with me again to schedule unless you wait too long. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, October 22, 2003 3:35 PM
To: Edward Donovan; aaf2@cwru.edu; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu
Subject: Re: COT Trial comments

Are you all available for a Conference Call tomorrow or Friday say around 12:00 PT or 3:00 Eastern Time?
Please let me know and I can do it from here.
Many thanks
Neil

----- Original Message -----
From: Edward Donovan
To: aaf2@cwru.edu ; higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
Sent: Wednesday, October 22, 2003 1:12 PM
Subject: Re: COT Trial comments

One problem with requiring "a lot" of blood gases is that clinicians and parents will view the study as "invasive" and this might inhibit enrollment. It seems to me that gases tend to be "one point in time" events that may or may not reflect overall well being of the infant. If there is no indwelling arterial catheter, I believe that the stick itself significantly alters gas exchange. Also, if the intervention only works with frequent blood gases, then it may be difficult to disseminate to the real world.

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> 10/17/2003 11:54:49 PM >>>
Hi
I have been on service and trying to avoid my email.
Well, success has a strange definition, we have pleased those that squeaked the loudest, and developed a protocol that may be acceptable to the Network while having sacrificed some major defining differences between the groups.
I would suggest that if we get the go ahead, we develop the study manual to include mandatory blood gases at least q 6 - 8 h for the first 48 hours, and force the extubation of the Treatment small infants by enforcing the current protocol - There is little squeak room here, they will all have study Pulse

oximeters by 1 hour and we will do a data dump at 72 hours, thus we will have the SpO2 at 1 hour. We have a data sheet that includes the actual FiO2 at 1 hour and a 1 hr blood gas.
In addition we follow Wally's suggestions regarding study monitoring. We can make a number of changes to the actual details and strengthen the differences. Please think about how to tighten this up. Once approved, the manual will be the protocol!!
We never mentioned blood gases as yet, that is not to say we are not going to insist on them.
We have allowed the use of Nasal SIMV, we also are advocates of that approach. I believe that the current protocol for the larger strata will be different as we have forced intubation of the Control infants for surfactant by 1 hr and not for the Treatment infants. Most centers do not do rapid extubation, and I doubt that they will now change. We would ask each site to file its current approach before the trial. Please give all this some thought.
Me. I am waiting to hear that we have been approved to move ahead. I indicated to Cynthia Cole that we were almost there and Massimo is moving ahead.
Wally. Masimo will have POs available within 4 - 6 weeks after we finalize the ranges. Cynthia seems to like our current limits as did Bill Hay. I will try to finalize.
Thanks for staying tuned.
Neil
----- Original Message -----
From: "Shahnaz Duara" <sduara@miami.edu>
To: "'Avroy A. Fanaroff'" <aaf2@po.cwru.edu>; "'Wally Carlo, M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Neil Finer'" <nfiner@ucsd.edu>; <higginsr@mail.nih.gov>; "'Avroy A. Fanaroff, M.D.'" <aaf2@cwru.edu>; "'Ed Donovan'" <Edward.Donovan@chmcc.org>
Sent: Friday, October 17, 2003 9:03 AM
Subject: RE: COT Trial comments

Dear All,

I agree with much of what Richard has to say. Unfortunately for the trial, we have struck a compromise situation which fits the 'comfort zone' of the many neonatologists who need to comply with the study. It doesn't hurt to have the Yale group and Abbott's group go on record as wanting more mandates to separate the study groups. If similar requests come in greater numbers, we have an opportunity to say that by 'popular request' we are adding some mandates. Will that fly with the majority?

Miami certainly feels that there should be more prescribing of what is allowed to happen subsequently to treatment group infants who remain intubated (appropriately) at 24 +/-2 hours - as the protocol stands, there is no given interval as to how often subsequent blood gases are to be done, and there is no weaning strategy. Centers who prefer to leave a baby intubated can spread out gas sampling, in addition to manipulating the vent settings, as Richard points out. This would certainly drift the two arms together, particularly for the smaller infants - the take home message would then be that CPAP as a primary treatment modality is untestable in the 24-25 week GA group prospectively.

We support and are able to do the trial as it stands, but feel it could be strengthened if it were tightened, so long as there was group

agreement for the importance of the additions and willingness to comply.

The world could never have been created in seven days if academic neonatologists had been involved.

Shahnaz

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Friday, October 17, 2003 9:59 AM
To: Wally Carlo, M.D.; 'Neil Finer'; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial comments

Hi
Good points made by Richard, but we have been through most of them before It is becoming apparent again how difficult it is to design an intervention trial - and given the current outcomes to be able to show a difference between two treatment arms.
As I reflect on this more and more I think that we have massaged the study design to the max and will be going around in circles if we start modifying it again.
The main strength of the trial may be the saturation groups - this still makes for a compelling trial.
Av
At 06:50 AM 10/17/2003, Wally Carlo, M.D. wrote:
>The solution is to have different CO2/pH targets before extubation as
>we have previously discussed. wally
>
>-----Original Message-----
>From: Neil Finer [mailto:nfiner@ucsd.edu]
>Sent: Thursday, October 16, 2003 7:22 PM
>To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer;
>higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
>Subject: Fw: COT Trial comments
>
>
>
>----- Original Message -----
>From: "Richard A Ehrenkranz" <richard.ehrenkranz@yale.edu>
>To: <nfiner@ucsd.edu>
>Sent: Thursday, October 16, 2003 2:50 PM
>Subject: Fwd: COT Trial comments
>
>
> > Neil:
> >
> > I am sorry if you got this email already, but it seemed to bounce
> > back.
> >
> > Richard
> >
> >
> > >Date: Thu, 16 Oct 2003 17:18:08 -0400
> > >To: Neil N Finer
> > >From: Richard A Ehrenkranz <richard.ehrenkranz@yale.edu>

> > >Subject: COT Trial comments
> > >Cc: Rosemary Higgins, Carolyn Petrie
> > >
> > >Neil:
> > >
> > >Members of my Division have reviewed the revised COT trial and I
> > >have had an opportunity to speak to most of them individually or in
> > >small groups. I have also received some written comments. I will
> > >summarize these comments:
> > >
> > >Our group is willing to participate in a RCT that seeks to evaluate
> > >a strategy that will increase survival without BPD at 36 weeks PMA.
> > >We are willing to change our current practice and administer
> > >surfactant in the
>DR
> > >and/or within 30 minutes of birth. However, we are concerned that
> > >the design of the current protocol will not demonstrate any
> > >difference
>between
> > >the study groups because we believe that, in clinical practice,
> > >there
>will
> > >be minimal difference between the proposed management plans. The
> > >major difference between the study groups for the 24-25 week strata
> > >is the forced extubation at less than 1 hour if a treatment arm
> > >infant meets extubation criteria; the re-intubation criteria are
> > >not that different. Since centers are to employ their usual
> > >resuscitation equipment for control infants in the 26-27 week
> > >strata, the management of control infants in centers (like ours)
> > >that use ventilators in the DR to provide PPV (with CPAP) may not
> > >be very different than the management of infants in the treatment
> > >arm. Even accepting the difference between the meaning of "may" vs
> > >"must," the criteria for intubation for surfactant, extubation, and
> > >re-intubation are not that different, making us wonder about the
> > >potential for manipulating FiO2 and ventilator settings to comply
> > >with the preference of the team rather than the protocol.
> > >Therefore, we question whether the study design will elicit
>any
> > >difference between these two treatment arms. In an effort to
> > >achieve clear differences between the study groups, we previously
> > >suggested that all control infants should be intubated in the DR,
> > >receive surfactant promptly and not be eligible for a forced
> > >extubation to CPAP or NSIMV.
> > >
> > >We are concurrently performing a trial in which intubated infants
> > >between 600-1250 g birth weight are given early surfactant and then
> > >randomized to NSIMV vs continued PPV. Our limited experience with
> > >the smallest infants makes us somewhat nervous about the forced
> > >extubation in the 24-25 weeks treatment arm strata. Almost all of
> > >the smallest infants have required re-intubation and prolonged
> > >ventilatory courses. We started this trial after Vineet Bhandari
> > >joined the group. He is a strong advocate of NSIMV and we had
> > >hoped it would give us some data to support it's use in this trial
> > >(which was already being discussed).
> > >
> > >We continue to have no difficulty with the SpO2 intervention.
> > >

> > >In summary, we would like to participate in this trial, but would
> > >like to feel that there is a distinct difference between the study
> > >arms.
> > >
> > >Richard
> > >
> > >
> > >
> > >_____
> > >Richard A. Ehrenkranz, MD
> > >Department of Pediatrics
> > >Yale University School of Medicine
> > >333 Cedar Street
> > >PO Box 208064
> > >New Haven, CT 06520-8064
> > >tele: 203-688-2320
> > >fax: 203-688-5426
> > >
> > >The information contained in this email may be privileged and
>confidential.
> > >If you are the intended recipient, you must maintain this message
> > >in a
>secure
> > >and confidential manner. If you are not the intended recipient,
> > >please notify the sender immediately and destroy this message.
> > >Thank you.
> >
> > _____
> > Richard A. Ehrenkranz, MD
> > Department of Pediatrics
> > Yale University School of Medicine
> > 333 Cedar Street
> > PO Box 208064
> > New Haven, CT 06520-8064
> > tele: 203-688-2320
> > fax: 203-688-5426
> >
> > The information contained in this email may be privileged and
>confidential.
> > If you are the intended recipient, you must maintain this message in
> > a
>secure
> > and confidential manner. If you are not the intended recipient,
> > please
>notify
> > the sender immediately and destroy this message. Thank you.
> >

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884
Fax 216-844-1479

From: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: Updated COT Trial
Date: Wednesday, October 22, 2003 4:19:38 PM

---

me too

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> 10/19/2003 5:52:18 PM >>>
Ok with me. wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Sunday, October 19, 2003 4:19 PM
To: Rosemary Higgins; Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer
Subject: Re: Updated COT Trial

Hi
This is a draft for Abbot. Please amend etc. I have NOT sent this to Abbot!! Hello Abbot I will try to answer your questions.
1) Staging in the 2 Strata. This may be an option, and it may help some sites. We would prefer to start both strata together. The criteria for intubation and extubation are similar between these strata and actually as the smaller infants all get prophylactic surfactant, this may be easier to manage. I will ask RTI if initiated the study at some sites for only 1 strata represents a problem.
2) We removed pH thinking that the sites were sending the message that we were too prescriptive. Reintubation is only mandated for the Control Infants, and we can certainly add the pH if you think that this is helpful. Will your group currently not re-intubate a baby with a $PaCO_2$ > 55 and an Oxygen requirement > 50% if the pH is > 7.25 but would if the pH was < 7.25? What pH are you currently using? Would they accept these criteria for the first 7-14 days? We could take the position that after the first 7 days re-intubation will be a local decision, and let the protocol separate the infants out by initial management.
3) The protocol says that repeat surfactant may be given and does not force the use of additional doses in either strata. We will ensure that this message is clearly stated in the final protocol and study manual.
4) Any form of CPAP may be used. We are hopeful that the bubble CPAP may be available by the time of the study initiation, but is has yet to receive FDA approval. I hope that these responses are helpful. Neil
----- Original Message -----
From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
To: <petrie@rti.org>; <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>; "Walid Salhab"

<Walid.Salhab@UTSouthwestern.edu>
Sent: Friday, October 17, 2003 5:44 PM
Subject: RE: Updated COT Trial

> Carolyn, Neil,
> Here is the feedback from the UT-Southwestern site. Almost everyone
> is on board and if I can get some good feedback on the following
> issues I think that this site will be in. There are 3 sticking points
> as followsn and the fourth point is minor:
>
> 1) Complexity of the intervention: Everyone agrees that this is a very
> complicated study that will be a challenge to do. Most everyone is
> ready to give it a try at this point but a few are very concerned
> about feasibilty given that within the ventilation arm of the study,
> there are in essence 4 groups (based on the 2 strata), and each has
> some specific issues. We would like to offer a potential solution
> which may appease many at this and other sites: Consider staging the
> initiation of the study such that for the first 4-6 months the study
> only enters infants in the 26-27 wk strata and subsequently the 24-25
> week strata is then initiated. This will allow people to get
> accustomed to the study in a group which may be more stable and with
> less problems, and take care of unanticipated problems which
> invariably will come up (as we encountered with the SAVE trial). This
> should help deal with the feasibiltiy issues that so many attendings
> are concerned about since it will be easier to focus on 2 groups
> within the ventilation arm rather than 4.
>
> 2) Re-Intubation Criteria: A number of people expressed concern that
> re-intubation criteria should have a pH associated with it if these
> criteria are to be extended over such a long time interval of 28 days.
> For example, at 14-28 days if we had an infant with a well compensated
> respiratory acidosis even with a high oxygen requriement, we would
> still try to keep the infant off the ventilator. This reflects the
> movement of this site to a more permissive strategy for right or wrong
> reasons. It is difficult to get people to move from this management
> (even though we have no data to say it is right) given that the
> intervention will prolong time on the ventilator. I thiink I have
> been successful in getting people to understand that it is critical to
> have separation between groups and maybe including a pH will obviate
> that. However, some further discussion regarding this issue would
> benefit our site.
>
> 3) Use of surfactant up to 72 hours: We will not give surfactant after
> 48 hours (we rarely give now after 36 hours) since it does not work
> well and we will be wasting the preparation. We are under heavy
> pressure to watch our costs and using surfactant at such a late
> post-natal age will not sit well with Administration since the study
> is so different from our practice. If other centers use it at 36-72
> hours of age, fine, but build in a window of time for surfactant use
> so we don't get dinged with violations for something we will not do.
>
> 4) Type of CPAP: Clarify what type of CPAP will be acceptable for the
> study and what type of equipment we will need.
>
> Hope this helps. I think this site is moving in the right direction.
> Sorry for the late response but by my watch it is still 10/17. AL

>
> >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> Reminder that today is the deadline for your comments:
>
>
> To the Neonatal Research Network Steering Committee:
>
> Attached is the latest COT trial for your input. Please send comments
> by Friday, October 17.
>
> Thanks!
>
> Carolyn
>
>
>
>

From: Wally Carlo, M.D.
To: "Lemons, James A"; Avroy A. Fanaroff; William Oh; edward.donovan@chmcc.org; Jobea0@chmcc.org; aaf2@cwru.edu; Higgins, Rosemary (NIH/NICHD); goldb008@mc.duke.edu; sshankar@med.wayne.edu; sduara@miami.edu; barbara_stoll@oz.ped.emory.edu; bkh@rti.org; petrie@rti.org; poo@rti.org; dstevenson@stanford.edu; nfiner@ucsd.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; abbot.laptook@utsouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
Subject: RE: Updated COT Trial
Date: Wednesday, October 22, 2003 12:42:17 PM

While the factorial design adds a second trial, it is important to notice that the clinicians will be masked to the saturation arm and will essentially not have to do much more regarding saturations that what would have to be done with a ventilation/CPAP trial. Regardless of the O2 intervention, O2 saturations would have to be kept in an agreed range for a ventilator/CPAP trial anyway. Therefore, I think we have a great opportunity to do two trials with less than twice the effort. It is also a very innovative approach, as for the first time we will be able to evaluate whether there may be an interaction between interventions to maintain adequate oxygenation and CO2 elimination. This has never been done on a ventilation trial. Wally

-----Original Message-----
From: Lemons, James A [mailto:jlemons@iupui.edu]
Sent: Wednesday, October 22, 2003 11:14 AM
To: Avroy A. Fanaroff; William Oh; edward.donovan@chmcc.org; Jobea0@chmcc.org; aaf2@cwru.edu; higginsr@mail.nih.gov; goldb008@mc.duke.edu; sshankar@med.wayne.edu; sduara@miami.edu; barbara_stoll@oz.ped.emory.edu; Wally Carlo, M.D.; bkh@rti.org; petrie@rti.org; poo@rti.org; dstevenson@stanford.edu; nfiner@ucsd.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; abbot.laptook@utsouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
Subject: RE: Updated COT Trial

I agree with you, Av. We also want to support this trial. However I still don't understand why we are making an already extremely challenging and complex trial of DR CPAP (which was our initial study) even more complex by adding a totally separate study with a separate primary outcome. Both may be important questions but this will just make it more difficult to obtain consent as we are having to explain two whole trials to parents in the midst of crisis. And they are totally separate studies, and I still believe should be done separately. Jim

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Tuesday, October 21, 2003 8:02 AM
To: William Oh; edward.donovan@chmcc.org; Jobea0@chmcc.org; aaf2@cwru.edu; Lemons, James A; higginsr@mail.nih.gov; goldb008@mc.duke.edu; sshankar@med.wayne.edu; sduara@miami.edu; barbara_stoll@oz.ped.emory.edu; wcarlo@peds.uab.edu; bkh@rti.org; petrie@rti.org; poo@rti.org; dstevenson@stanford.edu; nfiner@ucsd.edu; dale_phelps@urmc.rochester.edu; jon.e.tyson@uth.tmc.edu; abbot.laptook@utsouthwestern.edu; moshea@wfubmc.edu; richard.ehrenkranz@yale.edu
Subject: RE: Updated COT Trial

Hi
We all agree that it is a complex trial and all of Jim's points are valid.

However we have been working on this protocol for an extended period of time, we are tackling an important series of questions, and unless we can devise a better or simpler approach, which I believe is not possible, I am of the opinion that we should move forward with this trial. Neil and the committee have tried to accommodate everyone. I believe it is time to call the question. Alan is always reminding us that the Network was created to tackle the more complex questions. Our center is willing to give it our best shot.
Greetings
Av
At 06:04 AM 10/21/2003, William Oh wrote:
>Hi all: I totally agree with Jim's comments. On the other hand, this is
>an important trial and worth our efforts to carry it out.
>
>
>Bill
>
>
>
>William Oh, MD
>Professor of Pediatrics
>Brown Medical School
>Attending Neonatologist
>Women and Infants' Hospital
>Providence RI 02905
>Phone (Office) 1 401 274 1122 ext.1432
> (Fax) 1 401 453 7571
>
> >>> "Lemons, James A" <jlemons@iupui.edu> 10/20/03 17:34 PM >>>
>We still believe this is going to be an extremely difficult trial to
>implement and complete. This is due to the complexity of incorporating
>two separate trials with two separate primary outcomes into a singe
>factorial designed studey (for which the rationale is still unclear),
>as well as the short window for consenting. As challenging as
>enrollment has been for phototherapy because of the narrower window,
>enrollment for this trial will be extraordinarily challenging as the
>window is even tighter. And explaining this complex trial with two
>separate studies to parents under duress will require that much more
>time. This will be compounded for large centers with multiple sites
>and many more people involved. While we will attempt to support this
>trial if approved by the Steering Committe and outside reviewers, the
>logistical challenges of implementing and enrolling at reasonable rates
>we perceive as extremely difficult.
> Thanks, Jim
>
>-----Original Message-----
>From: Petrie, Carolyn [mailto:petrie@rti.org]
>Sent: Friday, October 17, 2003 1:27 PM
>To: 'M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu)'; 'M. D.
>Alan Jobe (Jobea0@chmcc.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)'; Lemons, James A; '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)'; 'Seetha Shankaran

>(sshankar@med.wayne.edu)'; 'William Oh2 (WOh@wihri.org)'
>Cc: 'aRose Higgins (higginsr@mail.nih.gov)'; Hastings, Betty J.;
>Petrie, Carolyn; Poole, W. Kenneth
>Subject: RE: Updated COT Trial
>
>
>
>Reminder that today is the deadline for your comments:
>
>
>To the Neonatal Research Network Steering Committee:
>
>Attached is the latest COT trial for your input. Please send comments
>by Friday, October 17.
>
>Thanks!
>
>Carolyn
>
>

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884
Fax 216-844-1479

From:	Neil Finer
To:	Wally Carlo, M.D.
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	Re: Updated COT Trial
Date:	Monday, October 20, 2003 10:41:58 AM

Agree
I will try to put together all the responses - I think that there were 4.
Neil
----- Original Message -----
From: "Wally Carlo, M.D." <WCarlo@PEDS.UAB.EDU>
To: "'Neil Finer'" <nfiner@ucsd.edu>; "Avroy A. Fanaroff, M.D." <aaf2@po.cwru.edu>; "Donovan, Edward (DONOVAEF)" <DONOVAEF@UCMAIL.UC.EDU>; "Shahnaz Duara" <sduara@miami.edu>
Sent: Sunday, October 19, 2003 2:51 PM
Subject: RE: Updated COT Trial

> Neil and all: I think we should probably get the feedback from all the
> centers together and discuss further changes with our committee and the
> opinion leaders as we had mentioned, otherwise, we will have a hard time
> getting to a consensus if we keep making changes to satisfy one group or
> another. Wally
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Saturday, October 18, 2003 7:17 PM
> To: Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara;
> Wally Carlo, M.D.; Neil Finer
> Subject: Fw: Updated COT Trial
>
>
> I will wait to hear from each of you before I respond to Abbot. Neil
> ----- Original Message -----
> From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
> To: <petrie@rti.org>; <nfiner@ucsd.edu>
> Cc: <higginsr@mail.nih.gov>; <bkh@rti.org>; <poo@rti.org>; "Walid Salhab"
> <Walid.Salhab@UTSouthwestern.edu>
> Sent: Friday, October 17, 2003 5:44 PM
> Subject: RE: Updated COT Trial
>
>
> > Carolyn, Neil,
> > Here is the feedback from the UT-Southwestern site. Almost everyone
> > is on board and if I can get some good feedback on the following
> > issues I think that this site will be in. There are 3 sticking points
> > as followsn and the fourth point is minor:
> >
> > 1) Complexity of the intervention: Everyone agrees that this is a very
> > complicated study that will be a challenge to do. Most everyone is
> > ready to give it a try at this point but a few are very concerned
> > about feasibilty given that within the ventilation arm of the study,
> > there are in essence 4 groups (based on the 2 strata), and each has
> > some specific issues. We would like to offer a potential solution
> > which may appease many at this and other sites: Consider staging the
> > initiation of the study such that for the first 4-6 months the study
> > only enters infants in the 26-27 wk strata and subsequently the 24-25

> > week strata is then initiated. This will allow people to get
> > accustomed to the study in a group which may be more stable and with
> > less problems, and take care of unanticipated problems which
> > invariably will come up (as we encountered with the SAVE trial). This
> > should help deal with the feasibiltiy issues that so many attendings
> > are concerned about since it will be easier to focus on 2 groups
> > within the ventilation arm rather than 4.
> >
> > 2) Re-Intubation Criteria: A number of people expressed concern that
> > re-intubation criteria should have a pH associated with it if these
> > criteria are to be extended over such a long time interval of 28 days.
> > For example, at 14-28 days if we had an infant with a well compensated
> > respiratory acidosis even with a high oxygen requriement, we would
> > still try to keep the infant off the ventilator. This reflects the
> > movement of this site to a more permissive strategy for right or wrong
> > reasons. It is difficult to get people to move from this management
> > (even though we have no data to say it is right) given that the
> > intervention will prolong time on the ventilator. I thiink I have
> > been successful in getting people to understand that it is critical to
> > have separation between groups and maybe including a pH will obviate
> > that. However, some further discussion regarding this issue would
> > benefit our site.
> >
> > 3) Use of surfactant up to 72 hours: We will not give surfactant after
> > 48 hours (we rarely give now after 36 hours) since it does not work
> > well and we will be wasting the preparation. We are under heavy
> > pressure to watch our costs and using surfactant at such a late
> > post-natal age will not sit well with Administration since the study
> > is so different from our practice. If other centers use it at 36-72
> > hours of age, fine, but build in a window of time for surfactant use
> > so we don't get dinged with violations for something we will not do.
> >
> > 4) Type of CPAP: Clarify what type of CPAP will be acceptable for the
> > study and what type of equipment we will need.
> >
> > Hope this helps. I think this site is moving in the right direction.
> > Sorry for the late response but by my watch it is still 10/17. AL
> >
> > >>> "Petrie, Carolyn" <petrie@rti.org> 10/17/03 1:27:08 PM >>>
> > Reminder that today is the deadline for your comments:
> >
> >
> > To the Neonatal Research Network Steering Committee:
> >
> > Attached is the latest COT trial for your input. Please send comments
> > by Friday, October 17.
> >
> > Thanks!
> >
> > Carolyn
> >
> >
> >
> >
>

From:	Wally Carlo, M.D.
To:	"Avroy A. Fanaroff"; "Neil Finer"; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	RE: COT Trial comments
Date:	Friday, October 17, 2003 12:16:14 PM

I think the details in response to Richard's comments could be addressed working with the to be designated opinion leaders. Wally

-----Original Message-----
From: Avroy A. Fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Friday, October 17, 2003 8:59 AM
To: Wally Carlo, M.D.; 'Neil Finer'; Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial comments

Hi
Good points made by Richard, but we have been through most of them before It is becoming apparent again how difficult it is to design an intervention trial - and given the current outcomes to be able to show a difference between two treatment arms.
As I reflect on this more and more I think that we have massaged the study design to the max and will be going around in circles if we start modifying it again.
The main strength of the trial may be the saturation groups - this still makes for a compelling trial.
Av
At 06:50 AM 10/17/2003, Wally Carlo, M.D. wrote:
>The solution is to have different CO2/pH targets before extubation as
>we have previously discussed. wally
>
>-----Original Message-----
>From: Neil Finer [mailto:nfiner@ucsd.edu]
>Sent: Thursday, October 16, 2003 7:22 PM
>To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer;
>higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
>Subject: Fw: COT Trial comments
>
>
>
>----- Original Message -----
>From: "Richard A Ehrenkranz" <richard.ehrenkranz@yale.edu>
>To: <nfiner@ucsd.edu>
>Sent: Thursday, October 16, 2003 2:50 PM
>Subject: Fwd: COT Trial comments
>
>
> > Neil:
> >
> > I am sorry if you got this email already, but it seemed to bounce
> > back.
> >
> > Richard
> >
> >
> > >Date: Thu, 16 Oct 2003 17:18:08 -0400
> > >To: Neil N Finer

> > >From: Richard A Ehrenkranz <richard.ehrenkranz@yale.edu>
> > >Subject: COT Trial comments
> > >Cc: Rosemary Higgins, Carolyn Petrie
> > >
> > >Neil:
> > >
> > >Members of my Division have reviewed the revised COT trial and I
> > >have had an opportunity to speak to most of them individually or in
> > >small groups. I have also received some written comments. I will
> > >summarize these comments:
> > >
> > >Our group is willing to participate in a RCT that seeks to evaluate
> > >a strategy that will increase survival without BPD at 36 weeks PMA.
> > >We are willing to change our current practice and administer
> > >surfactant in the
>DR
> > >and/or within 30 minutes of birth. However, we are concerned that
> > >the design of the current protocol will not demonstrate any
> > >difference
>between
> > >the study groups because we believe that, in clinical practice,
> > >there
>will
> > >be minimal difference between the proposed management plans. The
> > >major difference between the study groups for the 24-25 week strata
> > >is the forced extubation at less than 1 hour if a treatment arm
> > >infant meets extubation criteria; the re-intubation criteria are
> > >not that different. Since centers are to employ their usual
> > >resuscitation equipment for control infants in the 26-27 week
> > >strata, the management of control infants in centers (like ours)
> > >that use ventilators in the DR to provide PPV (with CPAP) may not
> > >be very different than the management of infants in the treatment
> > >arm. Even accepting the difference between the meaning of "may" vs
> > >"must," the criteria for intubation for surfactant, extubation, and
> > >re-intubation are not that different, making us wonder about the
> > >potential for manipulating FiO2 and ventilator settings to comply
> > >with the preference of the team rather than the protocol.
> > >Therefore, we question whether the study design will elicit
>any
> > >difference between these two treatment arms. In an effort to
> > >achieve clear differences between the study groups, we previously
> > >suggested that all control infants should be intubated in the DR,
> > >receive surfactant promptly and not be eligible for a forced
> > >extubation to CPAP or NSIMV.
> > >
> > >We are concurrently performing a trial in which intubated infants
> > >between 600-1250 g birth weight are given early surfactant and then
> > >randomized to NSIMV vs continued PPV. Our limited experience with
> > >the smallest infants makes us somewhat nervous about the forced
> > >extubation in the 24-25 weeks treatment arm strata. Almost all of
> > >the smallest infants have required re-intubation and prolonged
> > >ventilatory courses. We started this trial after Vineet Bhandari
> > >joined the group. He is a strong advocate of NSIMV and we had
> > >hoped it would give us some data to support it's use in this trial
> > >(which was already being discussed).
> > >
> > >We continue to have no difficulty with the SpO2 intervention.
> > >
> > >In summary, we would like to participate in this trial, but would
> > >like to feel that there is a distinct difference between the study

> > >arms.
> > >
> > >Richard
> > >
> > >
> > >
> > >_____
> > >Richard A. Ehrenkranz, MD
> > >Department of Pediatrics
> > >Yale University School of Medicine
> > >333 Cedar Street
> > >PO Box 208064
> > >New Haven, CT 06520-8064
> > >tele: 203-688-2320
> > >fax: 203-688-5426
> > >
> > >The information contained in this email may be privileged and
>confidential.
> > >If you are the intended recipient, you must maintain this message
> > >in a
>secure
> > >and confidential manner. If you are not the intended recipient,
> > >please notify the sender immediately and destroy this message.
> > >Thank you.
> >
> > _____
> > Richard A. Ehrenkranz, MD
> > Department of Pediatrics
> > Yale University School of Medicine
> > 333 Cedar Street
> > PO Box 208064
> > New Haven, CT 06520-8064
> > tele: 203-688-2320
> > fax: 203-688-5426
> >
> > The information contained in this email may be privileged and
>confidential.
> > If you are the intended recipient, you must maintain this message in
> > a
>secure
> > and confidential manner. If you are not the intended recipient,
> > please
>notify
> > the sender immediately and destroy this message. Thank you.
> >

Avroy A Fanaroff M.D.
Interim Chair of Pediatrics
RB and C Room 784
11100 Euclid Avenue
Cleveland, Ohio 44106-6003
E mail aaf2@cwru.edu
Phone 216-844-3884
Fax 216-844-1479

affiliates disclaim any responsibility for unauthorized disclosure of this information to anyone other than the addressee.

Federal and Ohio law protect patient medical information disclosed in this email, including psychiatric disorders, (HIV) test results, AIDs-related conditions, alcohol, and/or drug dependence or abuse. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Wally Carlo, M.D.
To: "Neil Finer"; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: RE: COT Trial comments
Date: Friday, October 17, 2003 6:57:28 AM

The solution is to have different CO2/pH targets before extubation as we have previously discussed. wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, October 16, 2003 7:22 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Fw: COT Trial comments

----- Original Message -----
From: "Richard A Ehrenkranz" <richard.ehrenkranz@yale.edu>
To: <nfiner@ucsd.edu>
Sent: Thursday, October 16, 2003 2:50 PM
Subject: Fwd: COT Trial comments

> Neil:
>
> I am sorry if you got this email already, but it seemed to bounce
> back.
>
> Richard
>
>
> >Date: Thu, 16 Oct 2003 17:18:08 -0400
> >To: Neil N Finer
> >From: Richard A Ehrenkranz <richard.ehrenkranz@yale.edu>
> >Subject: COT Trial comments
> >Cc: Rosemary Higgins, Carolyn Petrie
> >
> >Neil:
> >
> >Members of my Division have reviewed the revised COT trial and I have
> >had an opportunity to speak to most of them individually or in small
> >groups. I have also received some written comments. I will
> >summarize these comments:
> >
> >Our group is willing to participate in a RCT that seeks to evaluate a
> >strategy that will increase survival without BPD at 36 weeks PMA. We
> >are willing to change our current practice and administer surfactant
> >in the
DR
> >and/or within 30 minutes of birth. However, we are concerned that
> >the design of the current protocol will not demonstrate any
> >difference
between
> >the study groups because we believe that, in clinical practice, there
will
> >be minimal difference between the proposed management plans. The
> >major difference between the study groups for the 24-25 week strata

> >is the forced extubation at less than 1 hour if a treatment arm
> >infant meets extubation criteria; the re-intubation criteria are not
> >that different. Since centers are to employ their usual
> >resuscitation equipment for control infants in the 26-27 week strata,
> >the management of control infants in centers (like ours) that use
> >ventilators in the DR to provide PPV (with CPAP) may not be very
> >different than the management of infants in the treatment arm. Even
> >accepting the difference between the meaning of "may" vs "must," the
> >criteria for intubation for surfactant, extubation, and re-intubation
> >are not that different, making us wonder about the potential for
> >manipulating FiO2 and ventilator settings to comply with the
> >preference of the team rather than the protocol. Therefore, we
> >question whether the study design will elicit
any
> >difference between these two treatment arms. In an effort to achieve
> >clear differences between the study groups, we previously suggested
> >that all control infants should be intubated in the DR, receive
> >surfactant promptly and not be eligible for a forced extubation to
> >CPAP or NSIMV.
> >
> >We are concurrently performing a trial in which intubated infants
> >between 600-1250 g birth weight are given early surfactant and then
> >randomized to NSIMV vs continued PPV. Our limited experience with
> >the smallest infants makes us somewhat nervous about the forced
> >extubation in the 24-25 weeks treatment arm strata. Almost all of
> >the smallest infants have required re-intubation and prolonged
> >ventilatory courses. We started this trial after Vineet Bhandari
> >joined the group. He is a strong advocate of NSIMV and we had hoped
> >it would give us some data to support it's use in this trial (which
> >was already being discussed).
> >
> >We continue to have no difficulty with the SpO2 intervention.
> >
> >In summary, we would like to participate in this trial, but would
> >like to feel that there is a distinct difference between the study
> >arms.
> >
> >Richard
> >
> >
> >
> >_____
> >Richard A. Ehrenkranz, MD
> >Department of Pediatrics
> >Yale University School of Medicine
> >333 Cedar Street
> >PO Box 208064
> >New Haven, CT 06520-8064
> >tele: 203-688-2320
> >fax: 203-688-5426
> >

>

> _____
> Richard A. Ehrenkranz, MD
> Department of Pediatrics
> Yale University School of Medicine
> 333 Cedar Street
> PO Box 208064
> New Haven, CT 06520-8064
> tele: 203-688-2320
> fax: 203-688-5426
>

>

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT Trial
Date: Monday, October 13, 2003 8:31:20 AM

I vote in favor, wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 09, 2003 10:48 AM
To: Abbot Laptook (E-mail); Wally Carlo, M.D.; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Fanaroff Avroy (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; 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)
Cc: 'petrie@rti.org'
Subject: COT Trial

Hi,
Please send me your Steering committee vote for the COT trial by October 17, 2003. I have attached another copy of the protocol which was was sent to you on October 2.

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: Avroy A. Fanaroff
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT Trial
Date: Friday, October 10, 2003 10:31:56 PM

Hi
Vote Yes for COT trial
Thanks
Av
At 11:48 AM 10/9/2003 -0400, you wrote:

> Hi,
> Please send me your Steering committee vote for the COT trial by October 17, 2003. I have attached another copy of the protocol which was was sent to you on October 2.
>
> 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: Edward Donovan
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: Fw: Updated COT Trial
Date: Friday, October 10, 2003 2:36:50 PM

Ed
I am afraid to present any more options.
I'd like to hear from the centers, and if we can, live with the present version. It avoids the need to force the extubation, and this group should be a good test of CPAP versus surfactant.
I will yield to whatever our group wants.
Neil

----- Original Message -----
From: Edward Donovan
To: nfiner@ucsd.edu
Cc: Edward Donovan ; higginsr@mail.nih.gov ; sduara@miami.edu ; Wcarlo@peds.uab.edu ; aaf2@po.cwru.edu
Sent: Friday, October 10, 2003 11:19 AM
Subject: Re: Fw: Updated COT Trial

Neil,
The summary is helpful. Should we address the desire, in the 26-27 week treatment group infants, to intubate briefly to give surf. and immediately extubate to CPAP?
Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 10/09/2003 2:31:30 PM >>>

----- Original Message -----
From: "Neil Finer" <nfiner@ucsd.edu>
To: "Hastings, Betty J." <bkh@rti.org>; "'Barbara Stoll'" <barbara.stoll@oz.ped.emory.edu>
Cc: <higginsr@mail.nih.gov>; "Petrie, Carolyn" <petrie@rti.org>
Sent: Thursday, October 09, 2003 11:31 AM
Subject: Re: Updated COT Trial

> Agreed
> Here is a summary. Please review and see if this looks appropriate to
> circulate. Please feel free to modify. If you think this will help, then
> please circulate to the sites.
> Neil Finer
> ----- Original Message -----
> From: "Hastings, Betty J." <bkh@rti.org>
> To: "'Barbara Stoll'" <barbara.stoll@oz.ped.emory.edu>
> Cc: <higginsr@mail.nih.gov>; <nfiner@ucsd.edu>; "Petrie, Carolyn"

> <petrie@rti.org>
> Sent: Thursday, October 09, 2003 7:03 AM
> Subject: RE: Updated COT Trial
>
>
> > I agree. We should have that for each new protocol. I'll check with Neil
> > about this.
> > Thanks.
> >
> > -----Original Message-----
> > From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
> > Sent: Thursday, October 09, 2003 9:46 AM
> > To: Hastings, Betty J.
> > Cc: M. D. Neil Finer (nfiner@ucsd.edu); higginsr@mail.nih.gov; Petrie,
> > Carolyn
> > Subject: Re: Updated COT Trial
> >
> >
> > Betty -- It will be very helpful for colleagues if a brief summary is
> > included as well as the schema Thanks BJS
> >
> > "Hastings, Betty J." <bkh@rti.org> writes:
> > >I will be sending a final protocol (format, put correct date, etc) once
> > >Neil give me the "final" okay. Thanks.
> > >Betty
> > >
> > >-----Original Message-----
> > >From: Barbara Stoll [mailto:barbara.stoll@oz.ped.emory.edu]
> > >Sent: Wednesday, October 08, 2003 5:31 PM
> > >To: Neil Finer
> > >Cc: Hastings, Betty J.; higginsr@mail.nih.gov
> > >Subject: Updated COT Trial
> > >
> > >
> > >Will there be a "final" protocol-- don't want to send many versions to
> > >busy faculty
> > >
> > >Thanks
> > >
> > >BJS
> >
>

From: Neil Finer
To: Michael Cotten
Cc: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Fw: COT comments
Date: Thursday, October 09, 2003 2:39:19 PM
Attachments: COT-comments10.8.doc

Hi Mike
I will await all the comments before changing the protocol. Thanks for your detailed review. Absolutely pursue a secondary. Could it be done on Cord blood? Sent a protocol over the next few weeks. I assume that we will not have final approval till then.
Neil
----- Original Message -----
From: "Michael Cotten" <cotte010@mc.duke.edu>
To: "Neil Finer" <nfiner@ucsd.edu>
Sent: Thursday, October 09, 2003 10:03 AM
Subject: COT comments

>
>
>
>
> Hi Neil.....a few comments...mostly editorial where there's slight
> discrepancies in numbers and timing of decision and procedure
> points...also, a few more comments (as if you hadn't waded through enough)
> on the extubation and intubation cut points...
>
> also...I'd like to write a secondary study that would ask for a
microsample
> of blood to do risk association for RDS severity and surfactant protein
> gene polymorphisms...I"ve collected the literature and think it would be
> intriguing....it could be included as a check off/opt out in the consent
> form, and would add about a page to the consent form for necessary
> regulatory language...do you think it's worth pursuing? (on service now,
> but could turn it around to the study subcommittee by next week...)
>
> thanks.
>
> mc
>
>
> (See attached file: COT-comments10.8.doc)
>

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

August 21, 2003

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

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[12]. 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[13]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[14] 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.

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.[15] 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[16]. 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[17]. 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[18]. 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.[19] 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)[20]. 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[21] 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[22], 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.[23] 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.[24] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[25]

There are currently no studies which have prospectively compared early 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.[26] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[27] 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. [28]

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.[29] 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.[303132] 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.[33] 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.[34]

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.[35 36] 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.[37] 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))[38]. 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).[39] 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%).[40] 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.[41] 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.[42]

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.[43] 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.[44] 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.[45] 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[46] 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 (≤ 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	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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 to 27 completed weeks (up to 27 6/7th) 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. 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 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) 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. I would expect this will be lower if those not to be resuscitated are discounted....

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 Treatment and Control infants of 24 to 25 weeks will receive prophylactic surfactant. In the 26 to 27 week strata, the Control infants ***may*** receive prophylactic surfactant in the DR but ***must*** receive surfactant if they met criteria, whereas all Treatment infants will be placed on CPAP/PEEP, 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.

TREATMENT Group : Early Extubation and CPAP

Protocol: (Need to add surfactant redosing criteria for this strata...if it's there in other strata)

Treatment Group – Delivery Room Management: 24 – 25 weeks Stratum. Infants will be intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth. (I don't know why you need a range...what if the team can get the tube in w/in five minutes? Why not just say up to 45 minutes? These infants will be extubated by 1 hour of age if they fulfill the criteria below for Extubation.

This approach will provide the more immature strata infants with the benefit of prophylactic or early surfactant

Treatment Infants - NICU Management: 24 - 25 weeks

All Intubated Treatment infants of 24-25 wks stratum ***must*** be extubated by 1 hour of age, **if** they meet the Criteria for Extubation, as outlined below. These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention

Extubation Criteria for 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)I looked at the last 10 24/25 week infants and the time of first gas....the range was 50 minutes to 2 hrs and 55 minutes....could you consider expanding this criteria to 90 minutes or two hrs?...it may be that we just need to be quicker at getting lines/gases....how often was the first gas obtained w/in one hour in the pilot?
- An indicated SpO2 ≥ 90% with an FiO2 ≤ 50%

Following extubation, 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 5-6 cm H20 or nasal SIMV add the PEEP of 5-6 cm H2O.

Subsequent Intubation Criteria for Treatment infants

Intubation ***May BE attempted 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) (will I really let a very tachypneic (e.g.RR > 80) kid w/ a PaCO2 of 63 and pH of 7.21 on cpap sit on cpap?...
- An indicated SpO2 ≥ 90% with an FiO2 ≥ 50%

These criteria will continue in effect for 28 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

Extubation Criteria for Intubated Infants in Treatment Group: 24 – 25 weeks stratum

An intubated Treatment infants either not able to be extubated at 1 hour, or reintubated ***MUST have extubation attempted within 24 hours if <u>all</u> 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 (CV or HFV? Should there be a difference for MAP cutpoints?), ventilator rate < 15 – 20 bpm (why the range again…why not just ≤ 20?), an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

IN the larger strata there is a longer duration left to clinicians' discretion for extubation:
"**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."

Justify the discrepancy between the extubation after re-intubation time limits (24 hrs vs. 24 – 48 hrs?)
The Courtney paper extubation criteria is:

"Extubation was required when infants' condition had been stable for 6 to 12 hours while they were receiving minimal ventilatory support (for synchronized intermittent mandatory ventilation, the FiO_2 was no more than 0.25 and mean airway pressure was no more than 5 cm of water; for high-frequency oscillatory ventilation, the FiO_2 was no more than 0.25 and mean airway pressure was no more than 7 cm of water). The difference of 2 cm of water in mean airway pressure was intentional, since the flow characteristics of the SensorMedics ventilator at 33 percent inspiratory time result in an alveolar mean airway pressure 1 to 2 cm of water below that recorded at the hub of the endotracheal tube.[29,30]"

for us, the "must extubate" cut point for the treatment group, is twice what was used on a good study, that study also showed a difference in Mean Airway Pressure dependent on which ventilator group…I would think that we should make some allowance/correction for HFV vs. CV parameters for extubation.

Delivery Room Management : Treatment Group – 26-27 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 ±15 (again,,,why the range?) 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 successfully 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 MAY be intubated and given surfactant (within the first 72 hours of life)

- An FiO_2 >.50 to maintain an indicated SpO2 ≥ 90% (using the altered Pulse Oximeters)
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- These criteria will continue in effect for 28 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

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, 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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

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.

We have removed pH from the intubation criteria to simplify the criteria, and because pH alone is not usually a single criteria for intubation. 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 provides a significant survival benefit.(this statement re-iterates, I think, the need to change the range for intubation timing in the DR)This approach will be used for all infants in the 24-25 wk strata, and ***may*** be used for Control infants of 26-27 week infants. Any Control infant who has not received prophylactic surfactant in the DR, infants of 24- 25 wks who could not or were not intubated, or infants of 26 – 27 wks, will receive early surfactant if they meet criteria.

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 Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth.

The treatment group is to be intubated: "Infants will be intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth." Needs to be made equal for the first intubation/surf as best practice…ie…is it 15 or 30 minutes?

Control Group - NICU Management: 24 – 25 weeks strata

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

Extubation Criteria for Intubated Control Group infants: 24 – 25 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr and/or pH > 7.25(arterial or capillary samples, if venous subtract 5 torr from PCO2)
- 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) (are there better extubation/intubation criteria from Courtney's HFV study for extubation from HFV?)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants. 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 > .50 with or without CPAP with a SpO2 < 90% using the study pulse oximeters

These criteria will continue in effect for a minimum of 28 days from birth.

(Note: We have increased the FiO2 that requires intubation to 0.5 from 0.4 and have removed the pH as a single criteria without a PaCO2. A Control infant who meets both criteria MUST be intubated for the first 28 days of life.
We have also added a 4 hour minimal window to allow for some flexibility.)

Control Group – Delivery Room Management : 26 – 27 weeks Stratum: Infants **MAY** be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant minutes if they meet the criteria listed below in the first 72 hours 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 72 hours of life.

- An FiO_2 >0.4 (should this be 0.50? see above note in yellow) to maintain an indicated SpO2 ≥ 90% using study oximeter
- The use of CPAP and an FiO2 > .30 (Once the FiO2 is > .30 the infant must be intubated and receive surfactant.this seems aggressive….I would usually say no lower than 0.40))
- A $PaCO_2$ > 55 torr (Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 ± 9.9 torr and the pH was 7.3 ± 0.1) We have removed the pH(arterial or capillary samples, if venous subtract 5 torr from PCO2)

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

Repeat surfactant administration may be given if the FiO2 is > 40% (I would argue this could be lower…isn't the package insert guidance FiO2 > 0,3 and MAP also a consideration (I know it is here at Duke)

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 allows the use of prophylactic surfactant for all any Control infant and forces the use of surfactant when an infant meets criteria, but will not force prophylactic surfactant for such infants.

The protocol will not allow the use of CPAP and > 30% oxygen within the first 72 hours of life for any control infant who has not been intubated and received surfactant.

Extubation Criteria for Intubated Control Group infants: 26 – 27 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) with a pH > 7.25
- 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 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

Re-intubation Criteria of Extubated Control Infants 26 – 27 weeks:

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 > .50 with or without CPAP with a SpO2 < 90% using the study pulse oximeters (can those of us using cannulas use the table from the Physiologic definition study to figure FiO2 based on FiO2 and flow rate?)

These criteria will continue in effect for a minimum of 28 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 28 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 28 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 28 days of life, following which current unit practice will dictate management.

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] (but the low is lower in the COT trial)As an added safety feature, the POs used in this trial will gradually revert to the actual SpO2 values at the high and low limits of the research interval 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).

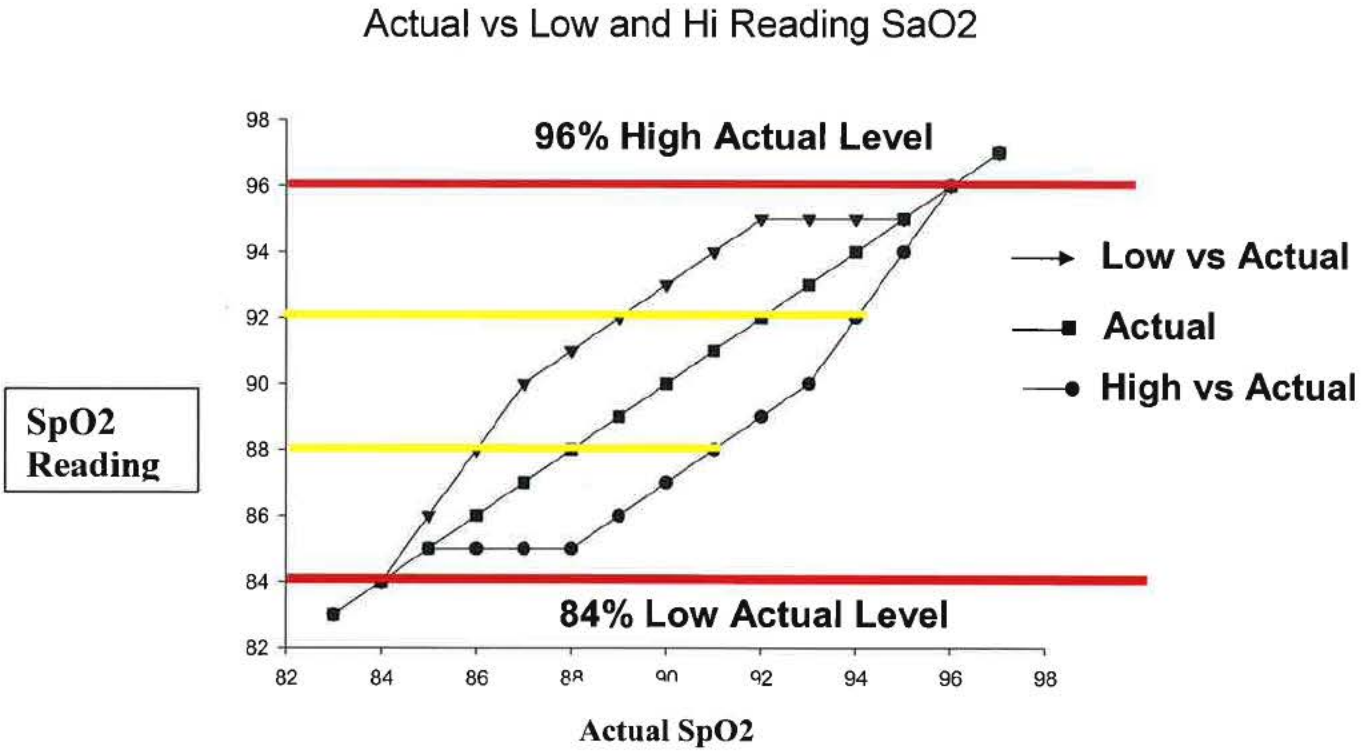
Table. Output and Actual SpO2 Targets and Alarms

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.[47,48,49]. 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.[50]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals. (what about redosing criteria listed in the first part of the protocol?)

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 26 – 27 wk 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)[51]
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 (seems like there's two primary analyses) 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 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.

13 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

14 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

15 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

16 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.

17 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.

18 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.

19 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.

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

21 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.

22 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

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

24 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.

25 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.

26 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.

27 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

28 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

29 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;

30 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

31 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

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

33 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

34 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

35 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

36 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

37 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

38 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

39 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

40 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.

41 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

42 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

43 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

44 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

45 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

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

47 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

48 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 .

49 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

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

51 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: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT Trial
Date: Thursday, October 09, 2003 2:12:31 PM

---

yes

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

>>> "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov> 10/09/2003 11:48:18 AM >>>
Hi,
Please send me your Steering committee vote for the COT trial by October 17, 2003. I have attached another copy of the protocol which was was sent to you on October 2.

Rose

Rosemary D. Higgins, M.D.
Program Scientist for the Neonatal Research Network
Pregnancy and Perinatology Branch
Center for Developmental Biology and Perinatal Medicine NICHD, NIH
6100 Executive Blvd., Room 4B03B
MSC 7510
Bethesda, MD 20892
(for Fed X use Rockville, MD 20852)
301-435-7909

301-496-3790 (FAX)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT Trial
Date: Thursday, October 09, 2003 12:43:09 PM

We vote YES
Neil Finer

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Abbot Laptook (E-mail) ; Carlo Waldemar (E-mail) ; Dale Phelps ; Ed Donovan ; Ehrenkranz Richard (E-mail) ; Fanaroff Avroy (E-mail) ; Jobe Alan (E-mail) ; Lemons Jim (E-mail) ; Michael O'Shea ; 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)
Cc: 'petrie@rti.org'
Sent: Thursday, October 09, 2003 8:48 AM
Subject: COT Trial

Hi,
Please send me your Steering committee vote for the COT trial by October 17, 2003. I have attached another copy of the protocol which was was sent to you on October 2.

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: "Neil Finer "
Cc: "Shahnaz Duara "; Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff, M.D. "; "Ed Donovan "
Subject: RE: COT Trial
Date: Tuesday, October 07, 2003 12:10:14 PM

Probably wait until you share other comments so they are not influenced by it. Wally

-----Original Message-----
From: Neil Finer
To: Wally Carlo, M.D.
Cc: Shahnaz Duara; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Sent: 10/6/2003 10:02 AM
Subject: Re: COT Trial

Thanks Wally
Once we have had comments back from the sites, I will proceed with this. Did you intend that we send this out now, or await the site comments? I have heard from 1 site who had a minimal grammatical type comment.
Neil

----- Original Message -----
From: Wally Carlo, <mailto:WCarlo@PEDS.UAB.EDU> M.D.
To: 'Neil Finer' <mailto:nfiner@ucsd.edu> ; Shahnaz Duara <mailto:sduara@miami.edu> ; higginsr@mail.nih.gov <mailto:higginsr@mail.nih.gov> ; Avroy A. Fanaroff, <mailto:aaf2@po.cwru.edu> M.D. ; Ed Donovan <mailto:Edward.Donovan@chmcc.org>
Sent: Saturday, October 04, 2003 7:08 AM
Subject: RE: COT Trial

Neil and everyone: My only major comment is that the protocol APPEARS to be complex. I make two suggestions:
1) Have a one page algorithm that can be used for each patient subgroup. It will be at the bedside for everyone to be able to use.
2) Have one of the research nurse be the "compliance officer" In charge of verifying compliance and giving feedback (together with the local "expert opinion leader") to clinicians twice a day. Clinicians may decide not to follow a specific part of the algorithm at selected times, but they would be aware of what the protocol calls for.
I think we need to make the trial easy for the clinicians and this compliance work will be easy for our research nurses, if appropriate time is allocated. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 25, 2003 6:43 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: COT Trial

Hello All
I haven't heard from anyone about these that I sent last Sunday. I am resending with minor corrections. There may have been a glitch in the email. I would appreciate your comments.

Regards
Neil

From: Wally Carlo, M.D.
To: "Shahnaz Duara"; "Neil Finer"; Higgins, Rosemary (NIH/NICHD); "Avroy A. Fanaroff, M.D."; "Ed Donovan"
Subject: RE: COT Trial
Date: Thursday, October 02, 2003 4:50:57 PM

With SAVe, we collected daily ABG data once a day closest (even plus or minus 12 hours) to noon. This was good, because optimization of protocol compliance can happen in the AM. Also, it was not requiered, but usually done in the sickest babies. Wally

-----Original Message-----
From: Shahnaz Duara [mailto:sduara@miami.edu]
Sent: Thursday, October 02, 2003 4:45 PM
To: 'Neil Finer'; Wally Carlo, M.D.; higginsr@mail.nih.gov; 'Avroy A. Fanaroff, M.D.'; 'Ed Donovan'
Subject: RE: COT Trial

Hi,

I looked through the Protocol and Powerpoint and think the changes capture most of what was suggested. I agree with Av that +/- 15 mins makes it more practicable. My concern remains the lack of blood gas frequency guidelines, once the initial gas is obtained for decision making. To reduce manipulation of study criteria, I suggest asking for a gas at least every 24 hours for the first 72 hours, and then every 2-3 days for babies who remain intubated in the Treatment arm and extubated/>RA (or >some low level O2) in the Control arm. I realize that this may be more than some centers are currently doing, but there's no other way of getting a CO2 sample - the last favorable sample may be held onto by folks with one or another bias (Abbot alluded to this on the conference call). The current bilirubin study requires us to get frequent bili samples upto 14 days, more than some of us would have ordinarily done. So, asking for a capillary or venous gas may well be acceptable to the sites and will help us monitor that the O2 AND CO2 criteria are being periodically re-evaluated fairly.

That's my contribution on this go around.
Hope your drive-thru heals well, Av (in Miami, drive-thrus don't usually escape so lightly...)

Regards
Shahnaz

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 25, 2003 7:43 PM
To: Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; higginsr@mail.nih.gov; Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: COT Trial

Hello All
I haven't heard from anyone about these that I sent last Sunday. I am resending with minor corrections. There may have been a glitch in the email. I would appreciate your comments.
Regards
Neil

computer.

From: Avroy A. Fanaroff
To: Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject: Re: COT Trial
Date: Thursday, October 02, 2003 3:52:43 PM

Hi
Few minor details- I think when you define the strata that we should be consistent so it is 24 and 0 /7weeks to 25 and 6/7 and 26 and 0/7 weeks to 27 and 6/7ths.
The AAP fetus and newborn committee has a statement on gestational age which is currently embargoed but I think that if you all abide by the embargo you can see it so I will forward it to you.
I wonder whether the time for initial intubation could be expanded from 30 plus minus 5 minutes to 30 plus minus 15 minutes.Our goal has been to give surfactant by 40 minutes and I think that we are inviting edits if we stick with 30 plus minus 5.
had drive by Herniorrhaphy yesterday - in at 7 am home by 11.30 am with general anaesthetic.
Not surprisingly a little sore today but should be back at work tomorrow.
Greetings
Av
At 12:28 PM 10/2/2003 -0700, Neil Finer wrote:

> ----- Original Message -----
> **From:** Neil Finer
> **To:** Higgins, Rosemary (NIH/NICHD)
> **Sent:** Thursday, October 02, 2003 12:26 PM
> **Subject:** Re: use of IVH data
>
> Rose
> I had sent out my revisions to the COT protocol to the Vent group. Av thinks its OK, and that if anything we are trying too hard. Have you reviewed. If it looks OK, I am ready to distribute to the Steering Group. I sent it out twice, the last being on Sept 25th. Please let me know if you are OK with this. I have attached the newest version with a brief Power Point of the actual ventilation intervention.I did send the SpO2 to the Post ROP group. I have had a positive response from Bill Hay, and no other replies. I am OK with circulating these to the Steering Committee for their feedback.
> Neil

24 – 25 week Strata

All Intubated for prophylactic Surfactant (within 30± 5 min)

Treatment Arm

Must **Extubate to CPAP**
At ≤ 1 hour If meets Criteria

FiO2 <.50 for SpO2 ≥ 90%
pH > 7.20
PaCO2 < 65 torr

Control Arm

May **Extubate**
Using *Any* one of Criteria

FiO2 < .40 for SpO2 ≥ 90%
pH > 7.25
PaCO2 < 55 torr
Mean airway pressure < 8 cm H2O,
Rate < 15 – 20 bpm,
If HFO, Amplitude < 2X MAP

26 to 27 week Strata

Treatment	Control
Delivery Room	
DR CPAP/PEEP Intubate only for Resus	MAY receive Prophylactic Surf
NICU	
Intubation Criteria May Intubate if meets ANY one of criteria	Control Infants not intubated in DR MUST be intubated for surfactant If meets ANY one of criteria < 72 hrs
FiO2 >.50 for SpO2 ≤ 90% PaCO2 > 65 torr	FiO2 >.40 for SpO2 ≤ 90% PaCO2 > 50 torr On CPAP and FiO2 > .30

Note – I have removed pH as criteria – Do you agree?

26 to 27 week Strata
Extubation Criteria

Treatment Must Extubate if meets all	Control May Extubate if meets any
PaCO2 < 65 torr	PaCO2 < 55 torr
pH > 7.20	pH > 7.25
FiO2 <.50 for SpO2 ≥ 90%	FiO2 < .40 for SpO2 ≥ 90%
MAP < 10 cm H2O,	MAP < 8 cm H2O,
ventilator rate < 15 – 20 bpm	ventilator rate < 15 – 20 bpm,
If HFV, amplitude < 2X MAP	If HFV, amplitude < 2X MAP

Both Strata
Re-intubation Criteria

Treatment

May Intubate if EITHER

$PaCO_2 > 65$ torr

$FiO_2 \geq 50\%$ for $SpO_2 \leq 90\%$

Control

Must intubate for EITHER
if persists > 4hours

$PaCO_2 > 55$ torr

$FiO_2 \geq .50$ for $SpO_2 \leq 90\%$
(On or off CPAP)

Please note that the FiO_2 criteria are similar.
Control infants MUST be intubated if they meet Either of these Criteria whereas Treatment infants MAY be intubated if they meet either of these criteria
These Criteria will be in effect for the first 28 days of life

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

August 21, 2003

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

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[12]. 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[13]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[14] 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.

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.[15] 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[16]. 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[17]. 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[18]. 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.[19] 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)[20]. 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[21] 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[22], 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.[23] 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.[24] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[25]

There are currently no studies which have prospectively compared early 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.[26] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[27] 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. [28]

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.[29] 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.[303132] 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.[33] 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.[34]

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.[35 36] 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.[37] 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))[38]. 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).[39] 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%).[40] 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.[41] 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.[42]

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.[43] 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.[44] 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.[45] 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[46] 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 (≤ 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	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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 to 27 completed weeks (up to 27 6/7th) 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. 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 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) 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 Treatment and Control infants of 24 to 25 weeks will receive prophylactic surfactant. In the 26 to 27 week strata, the Control infants ***may*** receive prophylactic surfactant in the DR but ***must*** receive surfactant if they met criteria, whereas all Treatment infants will be placed on CPAP/PEEP, 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.

TREATMENT Group : Early Extubation and CPAP

Protocol:

Treatment Group – Delivery Room Management: 24 – 25 weeks Stratum. Infants will be intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth. These infants will be extubated by 1 hour of age if they fulfill the criteria below for Extubation.

This approach will provide the more immature strata infants with the benefit of prophylactic or early surfactant

Treatment Infants - NICU Management: 24 - 25 weeks

All Intubated Treatment infants of 24-25 wks stratum ***must*** be extubated by 1 hour of age, if they meet the Criteria for Extubation, as outlined below. These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention

Extubation Criteria for 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%

Following extubation, 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 5-6 cm H20 or nasal SIMV.

Subsequent Intubation Criteria for Treatment infants

Intubation ***May BE attempted 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%

These criteria will continue in effect for 28 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, for example a higher FiO_2.***

Extubation Criteria for Intubated Infants in Treatment Group: 24 – 25 weeks stratum

An intubated Treatment infants 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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

Delivery Room Management : Treatment Group – 26-27 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 ±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 MAY be intubated and given surfactant (within the first 72 hours of life)

- An FiO_2 >.50 to maintain an indicated SpO2 ≥ 90% (using the altered Pulse Oximeters)
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- These criteria will continue in effect for 28 days from birth.

These are 'minimum' criteria meaning that such ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

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, 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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

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.
We have removed pH from the intubation criteria to simplify the criteria, and because pH alone is not usually a single criteria for intubation. 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 provides a significant survival benefit. This approach will be used for all infants in the 24-25 wk strata, and ***may*** be used for Control infants of 26-27 week infants. Any Control infant who has not received prophylactic surfactant in the DR, infants of 24- 25 wks who could not or were not intubated, or infants of 26 – 27 wks, will receive early surfactant if they meet criteria.

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 Infants will

be intubated in the delivery room and given surfactant within 15 minutes of birth.

Control Group - NICU Management: 24 – 25 weeks strata

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

Extubation Criteria for Intubated Control Group infants: 24 – 25 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr and/or pH > 7.25(arterial or capillary samples, if venous subtract 5 torr from PCO2)
- 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 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants. 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 > .50 with or without CPAP with a SpO2 < 90% using the study pulse oximeters

These criteria will continue in effect for a minimum of 28 days from birth.

(Note: We have increased the FiO2 that requires intubation to 0.5 from 0.4 and have removed the pH as a single criteria without a PaCO2. A Control infant who meets both criteria MUST be intubated for the first 28 days of life.
We have also added a 4 hour minimal window to allow for some flexibility.)

Control Group – Delivery Room Management : 26 – 27 weeks Stratum: Infants **MAY**

be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant minutes if they meet the criteria listed below in the first 72 hours 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 72 hours of life.

- An FiO_2 >0.4 to maintain an indicated SpO2 ≥ 90% using study oximeter
- The use of CPAP and an FiO2 > .30 (Once the FiO2 is > .30 the infant must be intubated and receive surfactant.)
- A $PaCO_2$ > 55 torr (Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 ± 9.9 torr and the pH was 7.3 ± 0.1) We have removed the pH(arterial or capillary samples, if venous subtract 5 torr from PCO2)

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 allows the use of prophylactic surfactant for all any Control infant and forces the use of surfactant when an infant meets criteria, but will not force prophylactic surfactant for such infants.

The protocol will not allow the use of CPAP and > 30% oxygen within the first 72 hours of life for any control infant who has not been intubated and received surfactant.

Extubation Criteria for Intubated Control Group infants: 26 – 27 weeks strata

Extubation ***MAY*** be attempted if ***ANY*** of the following criteria are present

- $PaCO_2$ < 55 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2) with a pH > 7.25
- 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 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

Re-intubation Criteria of Extubated Control Infants 26 – 27 weeks:
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 > .50 with or without CPAP with a SpO2 < 90% using the study pulse oximeters

These criteria will continue in effect for a minimum of 28 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 28 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 28 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 28 days of life, following which current unit practice will dictate management.

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).

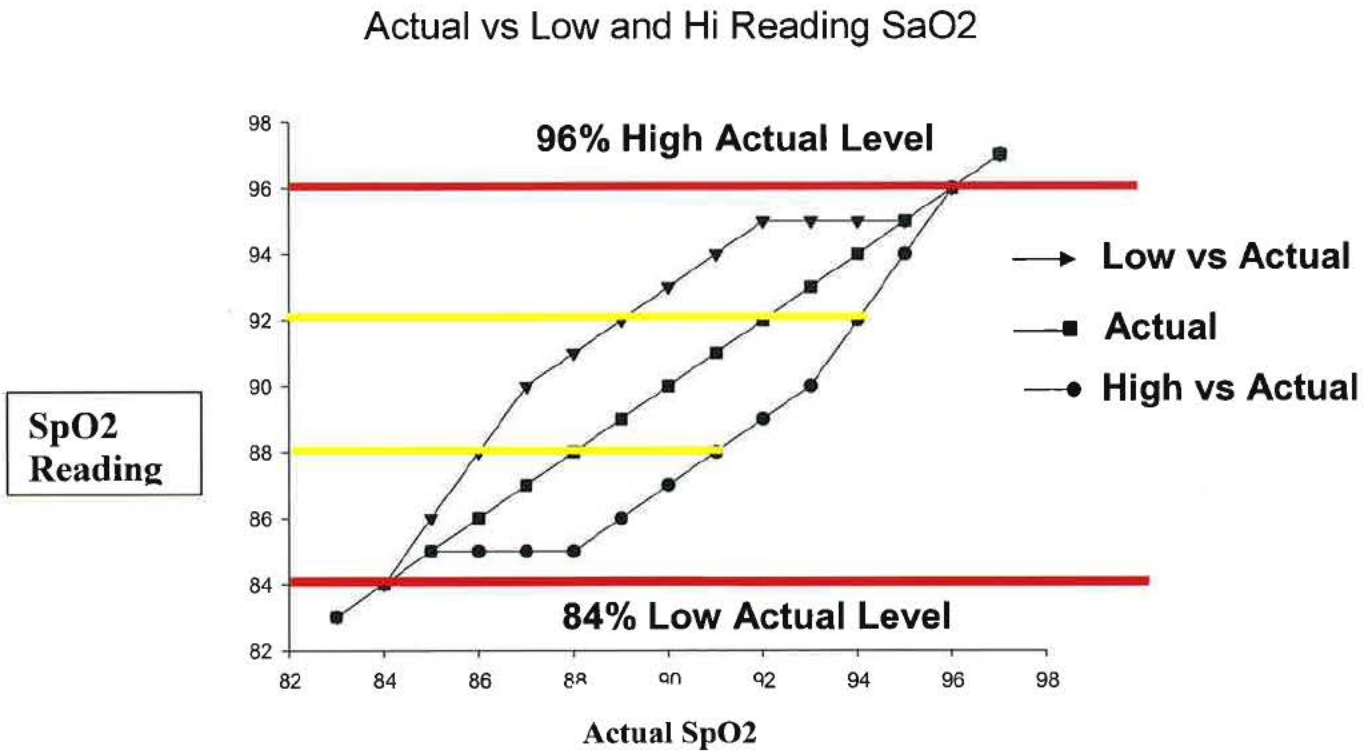
Table. Output and Actual SpO2 Targets and Alarms

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.[47,48,49]. 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.[50]

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)[51]
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 ≥ 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 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.

13 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

14 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

15 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

16 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.

17 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.

18 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.

19 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.

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

21 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.

22 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

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

24 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.

25 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.

26 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.

27 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

28 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

29 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;

30 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

31 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

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

33 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

34 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

35 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

36 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

37 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

38 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

39 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

40 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.

41 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

42 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

43 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

44 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

45 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

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

47 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

48 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 .

49 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

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

51 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:	Bill.Hay@UCHSC.edu; William Tarnow-Mordi
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan; bmackinnon@tufts-nemc.org; Kiani@masimo.com; Jhagadorn@tufts-nemc.org; Noden@emmes.com; Mpetters@masimo.com; Christian-F.Poets@med.uni-tuebingen.de; dale_phelps@urmc.rochester.edu; Dhs@perinatal.usyd.edu.au; Lisa.askie@perinatal.usyd.edu.au; CCole@tufts-nemc.org
Subject:	Re: Pulse Oximetry Working Group for POST ROP
Date:	Tuesday, September 30, 2003 9:26:14 PM
Attachments:	SpO2 Intervention COT and Post ROP Sept 30.doc

Hello Everyone
We have had detailed discussions about the SpO2 limits etc for the proposed Network COT Trial.
We have chosen the following - Low target range would be 85% to 89% and the High target range will be 91% to 95%. This is very close to your discussions.
Your current ranges would add 1% to each of our ranges.
We had agreed to come up with common ranges and so we would like your group to read over our methodology which I have attached for you. We would like to stay somewhat close to these levels, but we should have agreement. The Actual SpO2 and displayed SpO2 using our current suggestions, will be the same at 84% and below and 96% and above. The alterations occur within these limits. Please look this over and then let's discuss. Masimo is very keen to support these trials and we will begin testing the POs once we have agreement. The study POs will be able to display histograms to keep people on target, and these will be histograms of displayed values only. The real (actual) data will be available from the download. All values < 85% and > 95% will be actual. Masimo is working on this currently.
I hope that we can agree on low and high ranges and look forward to your responses.
Be well
Neil Finer
----- Original Message -----
From: "William Tarnow-Mordi" <williamt@westgate.wh.usyd.edu.au>
To: <Bill.Hay@UCHSC.edu>
Cc: <CCole@tufts-nemc.org>; <Lisa.askie@perinatal.usyd.edu.au>; <Dhs@perinatal.usyd.edu.au>; <dale_phelps@urmc.rochester.edu>; <Christian-F.Poets@med.uni-tuebingen.de>; <Mpetters@masimo.com>; <Noden@emmes.com>; <Jhagadorn@tufts-nemc.org>; <nfiner@ucsd.edu>; <Kiani@masimo.com>; <bmackinnon@tufts-nemc.org>
Sent: Tuesday, September 30, 2003 5:09 PM
Subject: Re: Pulse Oximetry Working Group for POST ROP

>
> I take Bill Hay's points in their entirety, particularly that we are
> proposing a pragmatic comparison of outcomes using one reasonably
> discrete range versus another, as in the BOOST study.
>
> A further issue is how to meet the study review group's criticism that
> there are insufficient data on the safety of the lower end of the
> currently discussed range of 85- 96% functional SpO2.
>
> This is most expeditiously answered by proposing within the Planning
> Grant a Phase I / II safety study of about 60 patients, 30 per group,
> randomly assigned to 85 - 90 vs 91 - 96% SpO2 from birth until 32 weeks
> post menstrual age or in air for a week. Outcomes would include
> survival, major cerebral abnormalities on ultrasound, ROP, PDA and
> pulmonary damage (as opposed to oxygen requirement).

> This is a logical next step beyond the AVIOX study and would fit with
> the pilot study proposed in Australia.
>
> For this, we would need masked Masimo oximeters, programmed as
> previously agreed with Neil Finer's group.
>
> all the best
>
> William
>
>
> Bill.Hay@UCHSC.edu wrote:
>
> >I think the discussion about SpO2 ranges is getting too close to
> >splitting hairs. Pick a reasonable range, stick with it, spend time and
> >effort having study center coordinators and local PIs manage the nursing
> >care on the spot to maximize the outcome desired (and for the grant,
> >describe more specifically how this will be done). The study section
> >reviewers lack clinical experience, I think. That said, though, they are
> >right to ask for specific ranges and efforts to maximize achieving
> >these, but in reality, we are testing current instruments that are much
> >more capable of alarming truly when the limits are exceeded, so I think
> >this will be easier to do than it was with STOP-ROP.
> >
> >More philosophically, we should acknowledge to the study section
> >reviewers that we are not testing a form of treatment, rather we are
> >testing for outcomes of one reasonably discrete range of currently
> >measurable SpO2 values vs another, ranges that are within the over all
> >range of SpO2 values that preterm infants are treated with, to provide
> >information that is as accurate as current methods of measurement allow
> >for the clinician to better understand the risks vs benefits of
> >producing in this gestational age range of preterm infants one range of
> >SpO2 values vs another. This gets away from the tone of the reviewers
> >(one, at least) who seemed to assume that we were recommending a lower
> >value of SpO2 and were testing to prove that we are correct in our
> >recommendation.
> >
> >William W. Hay, Jr., MD
> >Perinatal Research Center
> >University of Colorado Health Sciences Center
> >13243 East 23rd Ave., Bldg. 260, MS F441
> >Aurora, Colorado 80010
> >Phone: 303-724-1600
> >Fax: 303-724-0898
> >Email: bill.hay@uchsc.edu
> >
> >
> >-----Original Message-----
> >From: Cole, Cynthia [mailto:CCole@tufts-nemc.org]
> >Sent: Friday, September 26, 2003 5:00 AM
> >To: Lisa Askie (E-mail); David Henderson Smart (E-mail); Dale Phelps
> >(E-mail); Hay Bill; Christian F. Poets (E-mail); Mike Petterson
> >(E-mail); Neal Oden (E-mail); James Hagadorn (E-mail)
> >Cc: nfiner@ucsd.edu; Joe Kiani (E-mail); William Tarnow-Mordi (E-mail);
> >bmackinnon@tufts-nemc.org
> >Subject: Pulse Oximetry Working Group for POST ROP
> >
> >Dear POST ROP Pulse Oximetry Working Group,
> >Good evening or morning! As noted in a recent email, I am sending to

> >each
> >"POST ROP working committee" a draft of issues that we need to resolved.
> >Attached is a memo only related to pulse oximetry. Your thoughts and
> >suggestions are necessary and appreciated. We will not have immediate
> >answers to each of these, but we should have carefully considered
> >responses
> >by November 1. Please list additional items that have been omitted in
> >this
> >first draft.
> >Thank you - Cynthia
> > <<Pulse Ox Planning Group Issues 092503.doc>>
> >
> >
> >
> >**********
> >Confidentiality Notice
> >**********
> > The information transmitted in this e-mail is intended only for the
> >person or entity to which it is addressed and may contain confidential
> >and/or privileged information. Any review, retransmission,
> >dissemination or
> >other use of or taking of any action in reliance upon this information
> >by
> >persons or entities other than the intended recipient is prohibited.
> > If you received this e-mail in error, please contact the sender and
> >delete the e-mail and any attached material immediately. Thank you.
> >
> >
> >
> >
>
> --
> William Tarnow-Mordi
> Professor of Neonatal Medicine
> University of Sydney
> Westmead Hospital and The Children's Hospital at Westmead
> Head of Neonatology
> Westmead Hospital Perinatal Centre
> Ph (0)2 9845 8911 or (0)2 9845 5555 and pager 08352
> Mobile 0407 016 564
> Fax (0)2 9845 7490
>
> ----------
> Come to Sydney March 15 - 18, 2004 for the Perinatal Society of Australia and New Zealand annual meeting at the Darling Harbour Convention Centre. See http://www.psanz.org/ for details.
>
> Join us on March 13 and 14, 2004, at the INIS Collaborators' meeting , Holme Building, University of Sydney (details - Anne Cust anne@ctc.usyd.edu.au).
>
> Come to the POST ROP and AVIOX COllaborators' Working Buffet Dinner 8.00 pm - 10.00 pm MOnday 15 March, venue to be announced.
> ----------
>
>
>
>
> _____
>

> This electronic message and any attachments may be confidential. If you
> are not the intended recipient of this message would you please delete the
> message and any attachments and advise the sender. Western Sydney
> Area Health Services (WSAHS) uses virus scanning software but excludes
> any liability for viruses contained in any email or attachment.
>
> This email may contain privileged and confidential information intended
> only for the use of the addressees named above. If you are not the
> intended recipient of this email, you are hereby notified that any use,
> dissemination, distribution, or reproduction of this email is prohibited.
If
> you have received this email in error, please notify WSAHS
> immediately.
>
> Any views expressed in this email are those of the individual sender
> except where the sender expressly and with authority states them
> to be the views of WSAHS.

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.

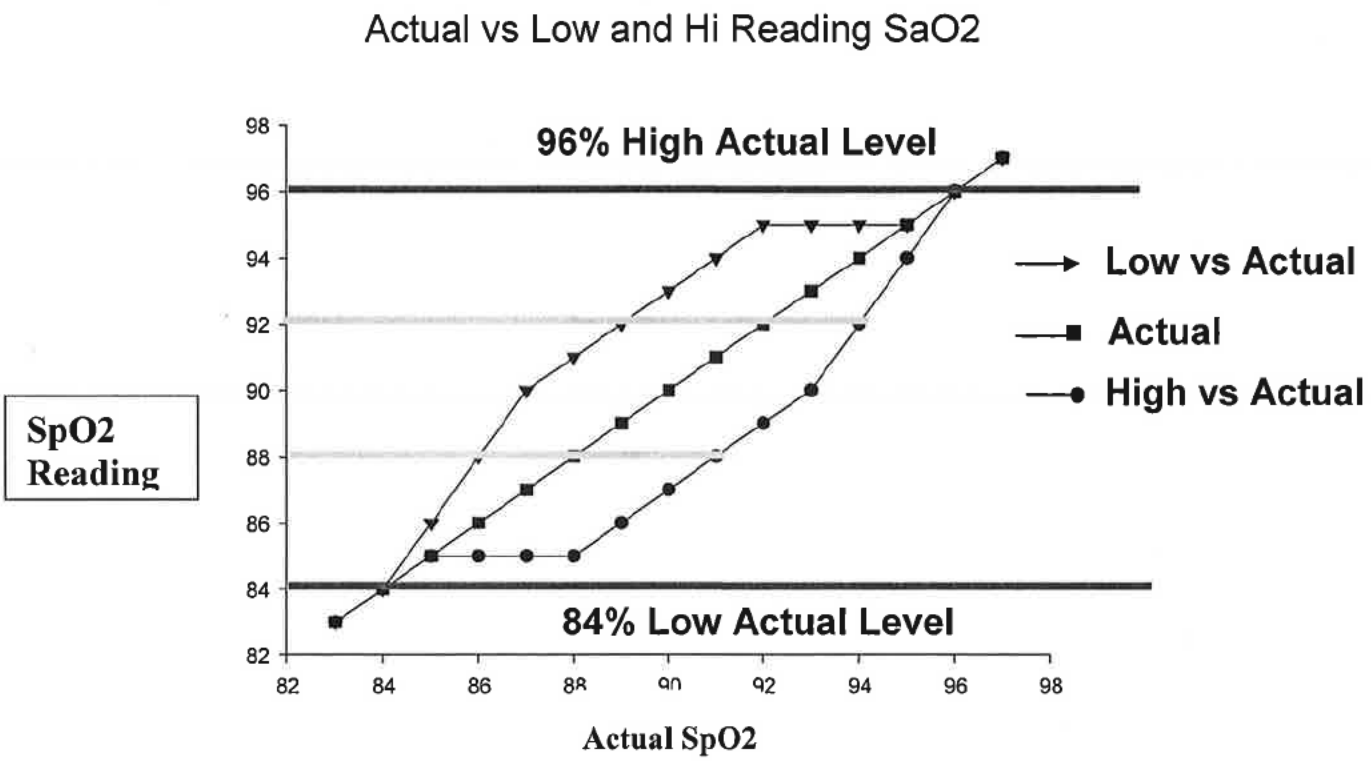
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.

From: Wally Carlo, M.D.
To: "Neil Finer"; Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT
Date: Thursday, September 18, 2003 12:46:32 PM

I think it is very improtant that we select BPD/death as the primary outcome. I think that the benefits of surf are evident in less deaths without an increase in BPD (and even a trend for a decrease). In a statistical analysis of this, we found (just abstract at SPR) that surf reduces deaths but these survivors tend to have BPD but those who were going to survive regardless, now do not get BPD.
On another related subject, I would prefer to only randomize infants who get surfactant as these are the ones most likely to get BPD and this approach would make enrollment and pre-enrollement much easier as we discussed yesterday. I think it is very important that we are sensitive to the difficulties other PIs are having with this early part of the trial, which may be unnecessarily complex. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 18, 2003 11:36 AM
To: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; higginsr@mail.nih.gov
Subject: Re: COT

Good day all

I agree that Alan was very helpful and forced people to fish or pull bait.
I think we need to discuss whether the primary for the Vent arm would change now that we are giving surfactant to all the small strata. The data regarding surfactant from the prophylactic review, some studies of which were pre antenatal steroids and none of which were at the current level of ANS use, including a single study which eliminated infants whose mothers received ANS > 24 hrs PTD (Kwong, 1985). While they reported a decrease in BPD or death, BPD alone was not different. In addition it was defined as the need for oxygen at 28 days.
Here's the actual quote from that review
"Bronchopulmonary Dysplasia: None of the individual trials support a difference in the incidence of bronchopulmonary dysplasia in all treated infants (not just survivors). For the purpose of these studies, bronchopulmonary dysplasia was defined as an oxygen requirement at 28 days of age. The typical estimate of the meta-analysis supports no difference in the risk of bronchopulmonary dysplasia (typical relative risk 0.93, 95% CI 0.80, 1.07; typical risk difference -0.03, 95% CI -0.09, 0.03)."
"a decrease in the risk of bronchopulmonary dysplasia or death (typical relative risk 0.84, 95% CI 0.75, 0.93; typical risk difference -0.10, 95% CI -0.16, -0.04. (Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review). In: ***The Cochrane Library***, Issue 3, 2003. Oxford: Update Software)
These studies were all 1991 or earlier, and not all found a decrease in BPD. In addition some of these studies gave prophylaxis versus control, and thus the control infants received no surfactant, and others allowed selective rescue.

The early surfactant trials defined early as 30 min, 1 or 2 hours, and 3 of the 4 trials were published in 1992.
Here CLD was used from 2 trials who used different definitions, only one of whom used oxygen at 36 weeks, and this study found no difference. Here is the actual description
"Gortner (1998) reported on the effect on chronic lung disease (CLD) of early selective surfactant administration. Gortner defined CLD as a requirement for supplemental oxygen at 36 weeks adjusted age. No significant effect of early surfactant treatment was noted (RR: 0.62, 95%CI 0.25, 1.53; RD: -0.03,

95%CI -0.08, 0.02). OSIRIS (1992) defined CLD as a supplemental oxygen requirement at the "expected delivery date," and showed a significant reduction in risk of CLD associated with early surfactant treatment (RR: 0.70, 95%CI 0.55, 0.89; RD: -0.03, 95%CI -0.06, -0.01).The meta-analysis estimated a significant reduction in CLD with early selective surfactant treatment (Typical RR: 0.70, 95%CI 0.55, 0.88; Typical RD: -0.03, 95%CI -0.05, -0.01)
In addition the review comparing natural versus artificial surfactant, these studies being more recent (4 studies after 1997, 2 of these in 2000) reported any difference in the occurrence of CLD.(Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome (Cochrane Review). In: ***The Cochrane Library***, Issue 3, 2003. Oxford: Update Software
"Chronic lung disease (oxygen requirement at 36 weeks adjusted age): Prevention trials: Hudak 1997 reports no significant effect of surfactant preparation on the risk of chronic lung disease (RR 1.09, 95% CI 0.90, 1.31; RD 0.03, 95% CI -0.03, 0.09). Treatment trials: None of the four trials that report on the incidence of chronic lung disease note an effect of surfactant preparation on the risk of chronic lung disease. The meta-analysis of the treatment studies demonstrates no effect of surfactant preparation on the risk of chronic lung disease (typical relative risk 0.97, 95% CI 0.85, 1.11; typical risk difference -0.01, 95% CI -0.04, 0.03).Overall, the meta-analyses support no significant effect of surfactant preparation on the risk of chronic lung disease (typical relative risk 1.01, 95% CI 0.90, 1.12; typical risk difference 0.00, 95% CI -0.03, 0.03).

I am raising this issue as I expect some to think that as we have changed the protocol, we should alter our expectation regarding the incidence of CLD. I would argue that the current data available suggests that surfactant use, either prophylactic or early is not a significant risk factor for the occurrence of CLD using data from RCTs. Thus I believe that the major effect will be on the difference in the ventilation approach, pushing us to have a clear strategy and a difference in the 2 arms. I am happy that we have that, and that neither population is at increased risk. I would therefore argue that our sample size is adequate, and does not need to be changed.
When we have agreement on the actual protocol I will put some of this in the preamble portion. I would appreciate your thoughts, comments, and your view of the current evidence.
Regards
Neil

.----- Original Message -----

From: Wally Carlo, M.D.
To: 'avroy a fanaroff' ; Edward Donovan ; Edward Donovan ; higginsr@mail.nih.gov ; sduara@miami.edu ; aaf2@cwru.edu ; nfiner@ucsd.edu
Sent: Thursday, September 18, 2003 7:56 AM
Subject: RE: COT

I think Alan statements were thoughtful (although quite balanced) and help people think straight. Neil: Thanks for your hard work. Wally

-----Original Message-----
From: avroy a fanaroff [mailto:aaf2@po.cwru.edu]
Sent: Thursday, September 18, 2003 12:22 PM

To: Edward Donovan; Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@cwru.edu; nfiner@ucsd.edu
Subject: Re: COT

Hi
Let me add my congratulations
Let's guess who voted NO but move forward with vim and vigor
Greetings
Av
At 09:36 AM 9/18/2003 -0400, Edward Donovan wrote:

> Neil,
> How about them apples?
> With everything else we have to do, I personally think that we should have some input into the budgeting process. The success of this trial will depend on costs that have not always covered in previous Network trial: L&D recruitment, DR interventions, 28 day interventions, high clinician education needs, ongoing individual subject compliance monitoring, etc.
> Let's go!
> 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: Wally Carlo, M.D.
To: "Edward Donovan"; Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: RE: COT
Date: Thursday, September 18, 2003 9:56:51 AM

I think this was a problem with SAVE that has never been discussed but we noticed it here by comparing the monitoring we do in our various vent trials. When monitoring has been twice a day, we have had the best results. I think this was underestimated in SAVE. I would include 15 min per baby twice a day for compliance monitoring and maybe even document it at least initially (but from the SAVE experience, it probably be planned to continue it). Wally

-----Original Message-----
From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]
Sent: Thursday, September 18, 2003 8:37 AM
To: Edward Donovan; higginsr@mail.nih.gov; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; nfiner@ucsd.edu
Subject: COT

Neil,
How about them apples?
With everything else we have to do, I personally think that we should have some input into the budgeting process. The success of this trial will depend on costs that have not always covered in previous Network trial: L&D recruitment, DR interventions, 28 day interventions, high clinician education needs, ongoing individual subject compliance monitoring, etc.
Let's go!
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: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Cc: "Neil Finer"; "Petrie, Carolyn"
Subject: cot
Date: Wednesday, September 17, 2003 4:30:42 PM

My vote is yes, now and in a week. Neil: Great job! Wally

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT
Date: Wednesday, September 17, 2003 4:30:31 PM

I vote that we proceed with the DR CPAP.
Neil Finer

From:	Neil Finer
To:	Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; abbot.laptook@utsouthwestern.edu; Jobea0@chmcc.org; aaf2@po.cwru.edu; 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; sshankar@med.wayne.edu; WOh@wihri.org; bvohr@wihri.org
Cc:	Hastings, Betty J.; Petrie, Carolyn
Subject:	Re: GOT Trial Critiques and current protoco
Date:	Wednesday, September 17, 2003 2:11:43 PM
Attachments:	New Treatment Approach Sept 17 03.doc

Hello Everyone
We will initiate our call in the Next 30 minutes The Vent Group has continued its dialogue and has considered all the input that we have received. We very much appreciate evryones' attention to this protocol. We have made a major modification to this protocol, which we hope would remove some of the concerns, and simplify the initial intervention, and subsequent management.
We are proposing that All Treatment Infants of 24 to 25 weeks be intubated in the DR and receive prophylactic surfactant followed by forced extubation by 1 hour. The criteria to allow continued intubation at that time are essentially the same as the previous criteria for intubation.
This change will provide prophylactic surfactant to the most vulnerable of infants, both Treatment and Control, and will then challenge the Treatment infants to be supported by CPAP. The reintubation criteria and other aspects of the protocol are identical.
I have attached a reworked Section 4.1 of the Protocol describing the Treatment infants for you perusal.
I look forward to our discussion
Regards
Neil Finer

4.1 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

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.

TREATMENT Group

Overview:

Treated infants of 24 to 25 weeks will receive prophylactic surfactant within 15 minutes of birth, and will be extubated at 1 hour unless they meet criteria for continuing Intubation. Infants of 26-27 weeks will receive DR CPAP/PEEP, and if intubated for resuscitation will receive surfactant in the DR. These infants will continue to be treated with CPAP and will be intubated and receive surfactant if they meet Criteria for Intubation.

Protocol:

Treatment Group –All infants in the 24-25 wks strata will receive prophylactic surfactant in the DR. Infants of 26-27 weeks will receive DR CPAP/PEEP. Infants will be resuscitated using whatever FiO2 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 H2O and a PEEP/CPAP of 7– 8 cm cmH2O.

This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant. Thus all infants of 24 to 25 wks in the Treatment and Control group will be intubated for prophylactic surfactant in the DR.

All Intubated Treatment infants (all infants in 24-25 wks strata and 26 to 27 wks infants who required intubation in the DR) must be extubated by 1 hour of age, unless they meet the **Criteria for Continuing/Initial Intubation**, as outlined below.

Following extubation, all non-intubated 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 5-6 cm H20 or nasal SIMV.

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.

Treatment Group – Delivery Room Management : 24 – 25 weeks Strata
Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth. These infants will be extubated by 1 hour of age unless they fulfill the **Criteria below for Continuing /Initial Intubation**

Delivery Room Management : Treatment Group – 26-27 wk Strata - 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 7– 8 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.

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 of 26 to 27 weeks may not be intubated for sole purpose of giving surfactant in the delivery room (DR). Infants who receive 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 60 $\pm$ 15 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant. Thus earlier intubation in the 26 to 27 week 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.

Treatment Infants who were not intubated in delivery room, infants of 26 to 27 weeks, and any 24 to 25 week infant who was not intubated in the DR (Infants who were unable to be intubated) **MUST** be intubated and receive surfactant if they meet the **Criteria below for Continuing/Initial Intubation**

Criteria for Continuing/Initial Intubation for Treatment infants: *These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention*

Infants ***must*** be extubated by 1 hour of age, unless they meet any of the following criteria.

Non-Intubated Treatment infants of 26-27 wks must be intubated and receive surfactant if they met these criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 $\geq$ 90% (using the altered Pulse Oximeters)
- A pH < 7.20 – 7.25 and/or an arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

For Treatment infants who are extubated, reintubation may be performed if the infant meets any of these above criteria.
These are 'minimum' criteria meaning that such intubation may be delayed according to clinician preference, for example a higher FiO_2.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Treatment Infants who remain Intubated or who are Re-intubated:

Extubation *MUST BE attempted within 24 hours if all of the following criteria are met:*

- $PaCO_2$ < 65 torr with a pH > 7.20 - 7.25, (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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

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.

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.***

From: Wally Carlo, M.D.
To: "Neil Finer"; Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT Revision
Date: Wednesday, September 17, 2003 1:30:10 PM

A solution is to include the 26-27 weekers only if they get surfactant. Most will and anyway if they do not get surfactant is because they do not need the vent and their risk for BPD/death is going to be low. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 17, 2003 11:47 AM
To: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; higginsr@mail.nih.gov
Subject: COT Revision

Hello All
I have redone the Treatment Group section as per our phone calls. Both Av and Shahnaz were of the opinion that we should provide prophylactic surfactant to all 24 to 25 week infants but retain the current protocol for the 26-27 weekers. I have thus rewritten it this way. As a fall back, we could give prophylaxis to all, but I would present it as written as our opening gambit. Please quickly read and let me know if there are needed changes. I will then e-mail to the Steering Comm so that they would have it before the phone call.
Thanks
Neil

From: Wally Carlo, M.D.
To: "Neil Finer"; Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT Revision
Date: Wednesday, September 17, 2003 1:28:27 PM

A solution is that 26-27 weekers could get into the trial once they get surfactant! Most will. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Wednesday, September 17, 2003 11:47 AM
To: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; higginsr@mail.nih.gov
Subject: COT Revision

Hello All
I have redone the Treatment Group section as per our phone calls. Both Av and Shahnaz were of the opinion that we should provide prophylactic surfactant to all 24 to 25 week infants but retain the current protocol for the 26-27 weekers. I have thus rewritten it this way. As a fall back, we could give prophylaxis to all, but I would present it as written as our opening gambit. Please quickly read and let me know if there are needed changes. I will then e-mail to the Steering Comm so that they would have it before the phone call.
Thanks
Neil

From: Neil Finer
To: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject: COT Revision
Date: Wednesday, September 17, 2003 12:47:13 PM
Attachments: New Treatment Approach Sept 17 03.doc

Hello All
I have redone the Treatment Group section as per our phone calls. Both Av and Shahnaz were of the opinion that we should provide prophylactic surfactant to all 24 to 25 week infants but retain the current protocol for the 26-27 weekers. I have thus rewritten it this way. As a fall back, we could give prophylaxis to all, but I would present it as written as our opening gambit.
Please quickly read and let me know if there are needed changes. I will then e-mail to the Steering Comm so that they would have it before the phone call.
Thanks
Neil

4.1 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

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.

TREATMENT Group

Overview:

Treated infants of 24 to 25 weeks will receive prophylactic surfactant within 15 miinutes of birth, and will be extubated at 1 hour unless they meet criteria for continuing Intubation. Infants of 26-27 weeks will receive DR CPAP/PEEP, and if intubated for resuscitation will receive surfactant in the DR. These infants will continue to be treated with CPAP and will be intubated and receive surfactant if they meet Criteria for Intubation.

Protocol:

Treatment Group —All infants in the 24-25 wks strata will receive prophylactic surfactant in the DR. Infants of 26-27 weeks will receive DR CPAP/PEEP. Infants will be resuscitated using whatever FiO2 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 H2O and a PEEP/CPAP of 7– 8 cm cmH2O.

This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant. Thus all infants of 24 to 25 wks in the Treatment and Control group will be intubated for prophylactic surfactant in the DR.

All Intubated Treatment infants (all infants in 24-25 wks strata and 26 to 27 wks infants who required intubation in the DR) must be extubated by 1 hour of age, unless they meet the **Criteria for Continuing/Initial Intubation**, as outlined below.

Following extubation, all non-intubated 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 5-6 cm H20 or nasal SIMV.

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.

Treatment Group – Delivery Room Management : 24 – 25 weeks Strata

Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth. These infants will be extubated by 1 hour of age unless they fulfill the **Criteria below for Continuing /Initial Intubation**

Delivery Room Management : Treatment Group – 26-27 wk Strata - 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 7– 8 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.

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 of 26 to 27 weeks may not be intubated for sole purpose of giving surfactant in the delivery room (DR). Infants who receive 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 60 $\pm$ 15 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant. Thus earlier intubation in the 26 to 27 week 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.

Treatment Infants who were not intubated in delivery room, infants of 26 to 27 weeks, and any 24 to 25 week infant who was not intubated in the DR (Infants who were unable to be intubated) **MUST** be intubated and receive surfactant if they meet the **Criteria below for Continuing/Initial Intubation**

Criteria for Continuing/Initial Intubation for Treatment infants: *These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention*

Infants ***must*** be extubated by 1 hour of age, unless they meet any of the following criteria.

Non-Intubated Treatment infants of 26-27 wks must be intubated and receive surfactant if they met these criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 $\geq$ 90% (using the altered Pulse Oximeters)
- A pH < 7.20 – 7.25 and/or an arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

For Treatment infants who are extubated, reintubation may be performed if the infant meets any of these above criteria.

These are 'minimum' criteria meaning that such intubation may be delayed according to clinician preference, for example a higher FiO_2.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Treatment Infants who remain Intubated or who are Re-intubated:

Extubation ***MUST BE attempted within 24 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20 - 7.25, (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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

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.

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.***

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu); M. D. Alan Jobe (Jobea0@chmcc.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. 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); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org); M. D. Betty Vohr (bvohr@wihri.org)
Cc:	Hastings, Betty J.; Petrie, Carolyn
Subject:	FW: GOT Trial Critiques and current protoco
Date:	Wednesday, September 17, 2003 12:13:36 PM
Attachments:	Response to Critiques of COT Protoco-CH revl.doc

To the Steering Committee regarding the proposed COT Trial:

The following are my major concerns regarding this protocol.
Attached are the rest of my comments (in blue) in reference to the specific questions.

- The main problem I see with with this protocol is not that it is complex, but that it attempts to study multiple management strategies at the same time. Given that the competing strategies are so varied and the confounders are many, the conclusions will likely be weak. For instance, the permissive approach, loosely defined as the acceptance of higher PaCO2s (PaCO2 > 65 with pH<7.20-7.25) and higher O2 (FiO2 > 50 to keep sats >90%) requirement before intervention will be compared to a "more conventional ventilatory approach". What is this? More conventional than what? What is "conventional"? Mechanical ventilation in itself is an important factor in the development of BPD. It is not possible to do this kind of study without clearly specifying what is the intervention , i.e. the "permissive approach" (whatever that might be, it needs to be defined by more than just CO2 values and include important determinants such as tidal volumes) and the control, ie. "conventional ventilation" (probably will need a survey to find out what ventilation strategies are currently being used). Not doing so risks repeating the experience of HFV vs conventional mechanical ventilation research, where most studies were criticized for not standardizing the control arm. Even if this study shows that CPAP + the "permissive approach" (as defined in the current protocol) is better than "conventional ventilation" (who knows what this means) + surfactant, this will not help clinicians to better care for their patients.

-- I would not electively extubate an ELBW infant with an active PDA or hemodynamically unstable, even if all the ventilatory/blood gases parameters were met as this protocol mandates:
Extubation Criteria for Intubated Infants in Treatment Group:
Attempt immediate extubation - within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation MUST BE attempted within 24 hours if all of the following criteria are met:
* PaCO2 < 65 torr with a pH > 7.20 - 7.25, (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 H2O, ventilator rate < 15 - 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
These criteria will continue in effect for 28 days from birth.

In fact, the evidence-based adult approach to extubation strongly supports minimal cardio-respiratory stability prior to attempting extubation (MacIntyre 2001). There is no such literature in babies, but the few studies that have looked into extubation protocols in children favor the same approach (Farias 2001). Why set up a high- risk fragile baby for failure knowing that it is very likely he/she will need reintubation at higher settings than prior to extubation (Veness-Mehan 1990)?

- I would strongly support protocol guided ventilator management such as that proposed by Durand: "optimizing lung inflation, avoiding both atelectasis and overdistension, tolerating moderate hypercapnia, maintaining oxygen saturation within a narrow range, and aggressively weaning toward extubation" provided that the infant is hemodynamically stable. Durand showed that this was feasible: "the protocols for ventilator management of VLBW infants, both with HFOV and with SIMV were easily implemented and consistently followed" in 7 tertiary-level intensive care nurseries (Durand 2001). I believe a study design that incorporates a standardized approach to mechanical ventilation will result in much more meaningful conclusions.
Challenging? You bet!, but I think it is worth the effort.

Response to Critiques of COT Protocol: Sept 14, 2003

Q. The feasibility of the study was a great concern for a number of reasons including the complexity of study design, the difficulties of obtaining consent for such a complex trial from women in extremely preterm labor, and the problems of identifying and enrolling study candidates at all hours (even though we have in house fellows or faculty every night).
This is of greatest concern with infants at 24 weeks gestation and the need to in essence know if an infant will be given "full resuscitation" prior to delivery (in order to randomize and have every thing prepared prior to delivery). For right or wrong, we do triage many infants at 24 weeks gestation and the determination to resuscitate is determined by the provider at the time of birth. In addition, it is very difficult to envision discussions with mothers about the issue of viability/use of resuscitation at this gestation, and simultaneously explaining a study of the scope and magnitude of COT. We cannot reconcile obtaining consent before delivery for a fetus that in our hospital may not be given care. The question of intention to treat, and what happens to an infant who has been consented, randomized, and then at delivery is not supported has not been answered. A related consent issue is the mother who comes to L & D and rapidly progresses to delivery before she can be consented. It is difficult to estimate the number of women who fulfill such criteria, but use of a waiver may help for this sub-group of study candidates.

A. We believe that this study is complex but doable by the Network. We have experience with pre-delivery consent and found that it worked well for the DR CPAP such that waiver was infrequently required (13/104). This population is usually consulted by Neonatology prior to delivery and we would use this opportunity to discuss the protocol and obtain consent.
The DR CPAP used a randomization by site by week which facilitated the randomization, but led to an imbalance. This would also require a separate randomization for the pulse oximeter, but that could be done by a phone call or envelope or pre-labeled POs. We can certainly discuss whether there is support for such a methodology, which would not separately randomize by strata, if it were to be kept simple. In addition this methodology does not allow for concealed randomization, but the use of envelopes or any other method still allows some time before the intervention where the team is aware of the selected approach. Using a site by week or day etc methodology also randomizes infants of multiple pregnancies to the same arm, which may be appealing to parents. In addition it is much less stressful for the resuscitation teams who would essentially approach all infants on their watch the same way. If we used a daily schedule, we would suggest that shift change in the morning would be the logical time to institute the next allocation.
We would anticipate using double sealed envelopes that would indicate the randomization to either Control/Prophylactic Surf or Treatment/CPAP and a second code indicating the number of the Pulse Oximeter to be applied within an hour of birth. The center would be supplied with a number of POs with unique identifying numbers. The

teams would be asked to have surfactant available for all such deliveries, as Treatment infants who require intubation for resuscitation will also receive surfactant in the DR. We have discussed a Waiver but believe that most IRBs may be reluctant in view of the lack of evidence indicating that CPAP and prophylactic surfactant are both evidence based and being used equitably by the sites. This issue however, can be further discussed, and as for DR CPAP, some sites may want to request a waiver. We would encourage such an application.

The delivery room interventions are very straightforward – All Control infants apart from those who appear stable < 30% in the 26-27 week strata – we will have conflict with the iNO to prevent BPD study with the kids less than 800 grams, as all require intubation and surfactant in the DR per that protocol. In addition, kids > 800 grams are routinely placed on CPAP in the DR if they have any signs of respiratory distress and are not intubated. For practical purposes, most of these babies will have at least some retractions and will be on CPAP anyways according to our protocol- are intubated for surfactant and taken to the NICU for continued ventilation and weaning. All Treatment infants receive CPAP/PEEP and may only receive surfactant in the DR if intubated for resuscitation. From DR CPAP we would anticipate that about 50% of the 24-25 week strata will be intubated in the DR and they will receive surfactant at that time. We are then providing an early window to give surfactant to the Treatment infants to provide them with the added benefit of this intervention. It should be noted that for DR CPAP which also enrolled at all hours, hat the coordinators were usually not in the DR.

The question is raised regarding an infant who is consented and randomized and then does not receive full treatment. We would suggest that they be analyzed as intention to treat, and would hope that these occurrences are few, and balanced between the arms. We have added a 15% attrition, which may deal with a small number of such situations. This did occur in DR CPAP, where care was withdrawn after resuscitation for a number of reasons. These infants were all included. If no resuscitation is provided, we will provide for an indication of this on the delivery room form, and discuss with Ken and RTI how to deal with these situations. This would be the category of consented, randomized and not treated, or consented, and not randomized depending on the circumstances.

Q"*control infants should all be intubated in the DR and receive surfactant within 15 minutes; forced extubation to NCPAP or NSIMV should not be permitted. We felt that such a design would permit the needed evaluation of DR-CPAP with prophylactic surfactant*"

A. We agree and this is the design with the exception that those not requiring > 30% Oxygen or CPAP by10-15 minutes could avoid intubation. For a cleaner design, intubation of all control infants would be better and evidence based, and avoid the need to consider subsequent intubation criteria for this group. This must be balanced by the knowledge that once intubated, these infants should then meet extubation criteria, which could result in longer intubation than is currently practiced in a given institution. We know that mechanical ventilation has risks (BPD, infection, etc.), especially if it is prolonged (Van Marter 2002). It is not in the child's best interest to prolong it beyond strictly necessary. There is no equipoise about that and it involves more than minimal risk. Besides, one of the goals of this study is to show that the intervention results in increased survival w/o BPD when compared to standard care, not that the intervention is better than unnecessarily prolonging mechanical

ventilation. This should be balanced by the fact that less Treatment infants would be intubated than are done as per current practice.

Q.With respect to the design, multiple faculty members had major reservations about foregoing prophylactic surfactant, particularly when the trial's current design would not allow a determination of whether CPAP/PEEP administered in the absence of prophylactic surfactant produces outcomes worse than CPAP/PEEP administered with prophylactic surfactant.

A. Our study is designed to answer the question of whether the use of early CPAP/PEEP followed by CPAP and a permissive approach will produce respiratory outcomes equivalent or better than prophylactic surfactant with a more conventional strategy. The VON trial will have 3 arms, one of which will be early Surf with extubation etc. We believe that the question that we have asked is as important as the question being posed, and we cannot ask every question in this trial. In addition, the Network does not currently uniformly provide prophylactic surfactant we do, and thus this trial may benefit any enrolled infant; in our unit all <800 gram babies get prophylactic surfactant. This is supported by the current literature. In fact, prophylactic surfactant given by 15 minutes improves survival. If anything, this protocol will decrease the number of babies that receive prophylactic surfactant in our unit. The practitioners of early CPAP believe that the use of early CPAP is as effective as surfactant, and this is borne out by the decreased use of surfactant at Columbia compared with Boston centers (Van Marter 2000), and a lower BPD rate. This hypothesis has not been tested prospectively, there is no information on neurodevelopmental follow-up. In addition there is animal data which indicates that early CPAP, especially at 8 cm H2O produces improvement in oxygenation equivalent to surfactant administration (Probyn et al, PAS 2002). Data in animals, not babies, not peer-reviewed.

Q."Given the evidence of the benefit of prophylactic surfactant, the complexity of the current design, the likely length of the study, and the high likelihood of protocol violations I would not favor the trial as currently designed.

A.This is an interesting comment because this and many other centers do not practice the use of prophylactic surfactant in the population being studied here, and this especially true for the infants of 26-27 weeks.

Q.The use of delivery room surfactant for the control group strata of 24-25 weeks represents a major practice change. There is concern regarding a long learning curve, working through the logistics of getting the surfactant to the delivery room, and the drain of resources on the NICU by the longer period of time and the additional personnel needed in the delivery room. Furthermore, in a delivery service that has on average 40 deliveries per day (and has had up to 87 in one day!!!), the issues of communication between Obstetrics and the NICU is not to be underestimated. The latter represents areas where we have limited control, and thus may limit our success of a major change in practice in the delivery room. We have been attempting (with good success) to provide early rescue surfactant and administer surfactant in the first hour of life. If we were to

combine a NICU/prophylaxis approach without using a CXR, we are pretty confident that surfactant could be given within 30-40 min following birth

A.This nicely presents the balance within the Network of the use or lack thereof of DR prophylactic surfactant. Wow!! This place could do the study by themselves!! We had many discussions about the relative benefits of prophylactic and early surfactant, and they have never been really tested against each other. Both are good, and most assume that prophylaxis is better, but many studies were pre antenatal steroids, and some were pseudo-randomized, so we probably do not have the final answer. In addition, prophylaxis overtreats with 40-60% of the infants who may not have reached rescue criteria, depending on the criteria. Early is usually less than 2 hours, selective was somewhere between 6 and 24 hours, and the references to the Cochrane data is shown

(Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software)

Q..*In assessing oxygen saturation goals, it was agreed that this is question of central importance but that the study would be meaningful only if there was great effort to regulate FiO2 and adhere to saturation goals.*

A.We partially agree, and believe that even if a great effort is not made, the groups will have significantly different SpO2 ranges, which may lead to significant outcome differences. It is possible that our different ranges are too close to each other, but we have chosen them to stay within the 85% to 95% that most are currently comfortable with. If our study shows a non-significant trend, a subsequent trial can evaluate different and perhaps more separate ones. The current oximeters used in clinical practice are not precise and have delays. Masking the oximeters will introduce even more room for errors. I am not sure our IRB will approve these masked oximeters.

Q.The highest rated design option was to eliminate the delivery room component (allowing faculty to routinely use both CPAP and prophylactic surfactant and to enroll infants after NICU admission) and use a factorial design to simultaneously assess

conventional vs. permissive (conservative) ventilation (with different criteria for intubation and extubation)

conventional vs. conservative saturation goals.

A.This design suggests that CPAP plus surfactant in the DR is the best approach, but this approach has never been tested by anyone. There is a belief that these may be equivalent interventions, as noted above. In addition, we would be selecting an approach used by almost no one in the Network, to our knowledge. Centers that use early CPAP tend to delay intubation for surfactant, and centers that intubate in the DR, may not be using CPAP, and if they did, would only be using it for the time prior to intubation.

Q.Conduct a 3 armed ventilation trial (adding group given DR CPAP + prophylactic surfactant) and eliminate the evaluation of different oxygenation saturation goals. This

was the 1st choice of one faculty member and the 2nd choice of 3 faculty members, though they were aware such a trial was in process outside the Network (but would probably not resolve the issue).

A.VON is pursuing such a methodology, and we wish them luck. Our trial is complex enough, novel, and will address different issues so as to be complimentary to the VON efforts.

Q.The need to define surfactant re-dosing criteria.
Is there any restriction on what kind of surfactant can be used

A.The following has been added to indicate "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.

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

Q.The need to initiate caffeine therapy early in the infants in the treatment arm

A.Agreed and we have added the following

"**Use of Caffeine**:

Caffeine may (should?) be administered 2 hours prior to planned extubation, and for any clinically significant apnea.

Q.The need to obtain consent prior to delivery for study patients and to randomize only those infants whose mothers had received at least one dose of antenatal steroids prior to delivery.

A.This has not been addressed and we are unclear whether this should be done. All infants are at risk for CLD and ROP< these infants even more so. Why should they be denied entry? Randomization should create an equal number of such infants, and no study to date regarding surfactant or post natal steroids and no Network study to our knowledge has use such a methodology.

Q.The factorial design of the trial was concerning because of two separate primary outcomes. The rationale for linking the two studies was unclear. Also the potential for having interactive effects which could not be quantified was concerning, particularly if those effects might mask a potential benefit of one of the interventions. If there is scientific rationale to look at the effect of DR CPAP/permissive ventilation and SpO2 ranges on death/BPD, that would make the case for the factorial design much stronger in our view.
There is a high chance that the study could be stopped early for one reason, to the detriment of the factorial designed second question.

A.We have discussed this issue with Ken and we believe that while this is a factorial by design, we are essentially prospectively enrolling infants into 2 simultaneous randomized trials, the interventions of which they would receive anyway in a non-random fashion. Note that the Network does not practice prophylactic surfactant, and there is little agreement about acceptable SpO2 ranges between centers. We will be able to evaluate additive effects, and if an interaction is powerful enough, we will clearly recognize it. Since we currently combine in some way these clinical approaches, addressing them through a clinical trial will result in balanced patient allocations to each of the 4 cells. The Network is somewhat concerned regarding the SAVE trial, but there is currently little if any evidence to suggest that any arm of this trial would be harmful. Indeed. There is potential benefit to each arm if one believes the current evidence in that prophylactic surfactant is an evidence based intervention, and higher SpO2 may decrease or increase severity of ROP (STOP-ROP, Tin et al), while lower SpO2 may decrease BPD (BOOST, STOP-ROP), and there is substantial interest and preliminary data supporting early CPAP.

Q.Many faculty felt that one of the most important questions is still the role of bubble CPAP

A.We agree and would like to use the Bubbleflow. We are discussing with Fisher&Paykel this possibility, and we may have to file an IND. They are trying to satisfy the FDA at present, and it is conceivable that this trial could produce some evidence toward that end. There is recent data that suggests that bubble CPAP offers no advantages to gas exhange (Morley et al PAS, 2003)

Q.Some faculty questioned the need for different intubation and extubation criteria the criteria for intubation (CO2 65 and extubation CO2 60) are hard to reconcile

A.We are trying to maintain a significant difference between the ventilation management protocol and use stricter criteria for the Treatment infants. There were inconsistencies in the PaCO2 and SpO2 criteria that we have removed, and now the intubation and extubation criteria are similar within a group. We have specified actual criteria to ensure such differences. One issue not previously addressed was unplanned extubation in the Control infants and we have now added the following

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 intubation criteria, apart from the need for CPAP, for more than 4 hours, intubation should be performed.

Q.Some faculty raised the issue that intubation/extubation criteria would change with the masked high and low sats and were concerned that this could affect the duration of ventilation or the timing of intubation.

A.We believe that the use of the Study SpO2 ranges would effect decisions by

only a 3-4% noted SpO2 difference and that there is currently a wide range of acceptable SpO2 and PaO2 that are utilized throughout the Network. We do not believe that the use of the study Pos with altered ranges will effect clinical decisions to a mjor degree, and the knowledge that values below 85% and above 95% are real will ensure that for these deviations all staff will know the real SpO2 value.

Q.It was strongly suggested that the COT committee consider dropping the oxygenation part of the study and concentrate on the CPAP component of the trial. Keep in mind that the Network feasibility study was for the CPAP trial alone. Also the experience from STOPROP trial should be reviewed to see whether the oxygenation component of the protocol is doable or not

A.As previously explained we currently vary the acceptable SpO2 between centers, and there is preliminary data that lower SpO2 may be better (Tin et al, Chow et al). Both STOP ROP ands BOOST studied infants > 32 weeks PCA or at pre-threshold (about 34 weeks PCA) and no study has prospectively evaluated early ranges of PaO2. With the blinding, we believe that this portion of the study is much easier than the ventilation intervention.

Q.How do we handle multiple gestations? Exclude, enroll all fetuses, enroll only one, if so which one

A.Frequently asked. In response we ask whether any Network study has enrolled multiples as a unit. We had asked about this during the design of the DR CPAP. We are comfortable with either method, and parents would probably prefer unit randomization, but that may introduce imbalance. This study should follow the general approach being taken for all current trials such as phototherapy which randomizes all multiples separately.

Q.How about dropping 24 and 25 weekers and expand gestation strata to 28 weeks. In other word, change inclusion criteria to 26/0 to 28 completed weeks.

A.The group at greatest risk and least well studied is the younger strata. We may be the only group willing to evaluate this group.

Q.Concerns were expressed regarding the permissive ventilation strategy. Is pH >7.20 for extubation realistic. It maybe better to give a range of perhaps, 7.20 – 7.25 to allow for some flexibility.

A.Done, and to demonstrate the differences in the Network between sites I have added a response from Cincinnatti
For study purposes, it is OK to wait for severe apnea or pH < 7.2 and pCO2 > 60 and fiO2 > 0.5 to intubate infants 24-28 weeks. 10 Yes 0 No 1 ?

Q.Same applies to the rate of ventilator for extubation in the treatment group. Rather than < 15, use a range of 15-20

A.Done

Q.*A couple of faculty members expressed serious concern about high O2 range of up to 95%. They would be willing to go along with 92 0r 93 % . It was pointed out that a paper in this week New England Journal showed better outcome in regards to oxygenation target at 91-94 % as compared to 95-98%. Should we consider dropping the range to 90-93, not 90-95% ?*

A. As discussed by Dale, the BOOST trial started at 32 weeks PCA, and the ranges chosen are somewhat arbitrary. There are no previous data to use for any chosen range and so we have tried to choose different ranges within the 85% to 95% range, based on previous data. We believe that most sites will want larger rather than narrower ranges for alarms and thus we are aiming to have significant differences within the 85% to 95% range.

Q.It was also suggested that the COT Committee performs a survey for current practice in regards to the intubation and extubation criteria and practices among centers with the goal of setting up criteria that are as close to current practice as possible.

A.We will loosely poll at the Steering Committee meeting. If further information is deemed helpful, it can be obtained. We are probably recommending criteria that do not exactly match any center's current practice, and that applies particularly to the Subcommittee members. These criteria are thought to represent a reasonable consensus, and maintain separation between the groups.

Q.The most consistent concern was a lack of standardization of modalities of therapy, and with acknowledgement of different delivery systems having different levels of effectiveness, the Network should strongly consider standardization of the CPAP device.

A.We will attempt to obtain the Bubbleflow for this trial as noted above. Attempting to use another apparatus for standardization would be expensive, and without any evidence basis.

Q.The group also voiced concern over the perceived 3 different aspects of management to be investigated in one trial; early CPAP vs intubation early, permissive vs more aggressive ventilation, and the factorial design for O2.

A.This is a complex trial, and the CPAP and permissive approach are part of a single strategy, much modified to be acceptable within the ranges of current Network strategies. This will be compared to prophylactic surfactant and a more conventional ventilatory approach. The longer we delay, the greater will be the

drift toward a more permissive approach by all centers without adequate evidence.

The main problem with this protocol is not that it is complex, but that it attempts to study multiple management strategies at the same time. Given that the competing strategies are so varied and the confounders are many, the conclusions will likely be weak. For instance, the permissive approach, loosely defined as the acceptance of higher PaCO2s (PaCO2 > 65 with pH<7.20-7.25) and higher O2 (FiO2 > 50 to keep sats >90%) requirement before intervention will be compared to a "more conventional ventilatory approach". What is this? More conventional than what? What is "conventional"? Mechanical ventilation in itself is an important factor in the development of BPD. It is not possible to do this kind of study without clearly specifying what is the intervention , i.e. the "permissive approach" (whatever that might be, it needs to be defined by more than just CO2 values and include important determinants such as tidal volumes) and the control, ie. conventional (probably will need a survey to find out what ventilation strategies are currently being used). Not doing so risks repeating the experience of HFV vs conventional mechanical ventilation research, where most studies were criticized for not standardizing the control arm. Just to know that CPAP + the "permissive approach" (as defined in the current protocol) is better than "conventional ventilation" (who knows what this means) + surfactant will not help clinicians to better care for their patients.

Q.With ongoing study in Benchmarking, there may be significant management practices that he committee may want to standardize for the study. We believe that failure to standardize "Benchmarking" findings or best care will obscure the results as mechanical ventilation and early NCPAP are only part of the multifactorial etiology of BPD.

A.By the initiation of this trial, benchmarking will be close to completion. We have tried to suggest a minimal of standardized approaches, and indeed are testing the comparability of prophylactic surfactant to early CPAP. The Network has been aware that prophylactic surfactant is an evidence based intervention, but this approach is not standardized within the Network. This study will force such an approach for the Control infants, and the results will aid in determining future best practice. There is no currently accepted standard care regarding SpO2 limits.

Q.Nasal CPAP delivered by high flow nasal cannulae is not considered but has become standard practice in many nurseries.

A.Nasal Cannula may deliver CPAP but it is unregulated and unmeasured, and we are not prohibiting its use for infants subsequent to the discontinuation of CPAP. We would not, however encourage its use till better studied.

Q.Concern was raised about the intubation criterion of an FiO2 0.50 to maintain an SpO2 ≥ 88%. We would not know this because the limits on the pulse ox for the low range is 85-89%.

A.We have standardized this criterion to a SpO2 > 90%, the midrange of the SpO2 target range for both groups, and thus the Actual SpO2 could be 87% or 93% approximately. There is some information that currently SpO2 values may be somewhat optimistic, and all caretakers will be aware if the actual SpO2 if the true SpO2 is < 85% or > 95%. This study is designed to determine if such lower limits are beneficial as suggested by Tin et al and Chow et al.

Q.Page 12 – The injunction that "extubation must be attempted within 12 ± 2 hours . . . would be difficult if your clinical judgment dictates otherwise. For instance, extubation criteria are met but the child has a ductus, is developing pulmonary edema and therefore at risk for pulmonary hemorrhage.

A.We have changed this to a 24 hour period to allow more flexibility, and not force extubation, and re-intubation may delayed for up to 48 hrs

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 24 hours if all of the following criteria are met: I would not electively extubate an ELBW infant with an active PDA or if hemodynamically unstable, even if all the ventilatory criteria were met. In fact, the evidence-based adult approach to extubation strongly supports minimal cardio-respiratory stability prior to attempting extubation. There is no such literature in babies, but the few studies that have looked into extubation protocols in children favor the same approach. Why set up a high- risk fragile baby for failure knowing that it is very likely he/she will need reintubation at higher settings than prior to extubation?***

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. ***The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.***

Q.Permissive ventilation adds another confounder into the study and may cloud the outcome. It is another approach that needs to be validated. This may be further exacerbated by statements like "the minimum" criteria proposed on page 13 (i.e., intubation may be delayed according to clinical preference).

A.The Network would agree that permissive hypercapnia needs further testing. The SAVE trial was an attempt and the COT trial would provide adequate power to answer this question. The treatment group is intended to allow less intubation and less exposure to ventilation and determine if this approach is effective in reducing BPD. In our unit the effect will likely be the opposite: infants will receive surfactant later, therefore increasing the risk of having more lung injury; this

associated with conservative extubation criteria in the treatment group will likely result in longer exposure to ventilation.

Q.Protocol violations will be extremely common. Particularly night crews changing ventilation
Concern was raised about the time and monitoring of such a complex study to assure that compliance is high. The results of the feasibility trial (re: compliance) were not convincing given the limited time and intervention relative to the COT trial. There will need to be a hard look at what is needed in terms of Network Coordinator/PI time to realistically facilitate this study. The level of interaction that may be necessary between study personnel and attending staff is such that there may be negative spill-over to other Network endeavors (the latte is my personal concern).

A.We believe that the current iteration is somewhat simpler, and that additional surveillance may be required as suggested from Alabama
"There is concern about the need to monitor compliance and the agreement is that there will be a need to have a research coordinator assess protocol compliance twice daily with twice daily feedback (at least initially) to the caretakers (and PI/designated opinion leader as needed). This should be budgeted into the capitation".

Q.Allowing use of the Neopuff in the control group will reduce the potential differenced between the groups, making the testing of CPAP/EEP in the DR invalid

A. We hope that most of the control infants will be intubated in the DR for surfactant and the continuing use of CPAP in such infants will constitute a criteria for intubation. Therefore the use of the Neopuff would not confuse this trial. The Treatment infants will not be intubated in the DR except for resuscitation intervention. In addition, this trial is to evaluate a total approach involving early CPAP and a continuing permissive approach, not just the use of CPAP/PEEP in the DR. Even the DR CPAP feasibility trial was not powered to evaluate the benefit of DR CPAP.

Q.What will you do about kids who need to have upper and lower saturations looking for shunting?

A.Do what you normally do which is to drive the SpO2 > 96-98% and look for pre vs Postductal shunting. We will ensure that for such purposes and second identically altered PO will be available for such an evaluation. Any pre- vs post ductal difference will be noted, and all values > 95% are actual.

Q.Can you randomize an infant into the oxygen study if he is missed consent for the DR management portion of the trial? (or if the parents refuse that part?)

A.Not with the current design.

Q.You need some criteria to allow for intubation for some degree of excessive work of breathing

A.What is the data to support this request? We believe that we need to use objective criteria as are listed. Clinicians will make the ultimate decision, and we may have to analyze how often this happens.

Q.What if you don't have arterial gases? how do you use PaCO2 values? pH ? use VBG or CBG?

A.In the absence of an arterial line, a capillary sample is preferred, but venous values may be used, and should be interpreted as reading 5 torr higher than the arterial PaCO2. This has been added to the protocol

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: GOT Trial Critiques and current protoco
Date: Wednesday, September 17, 2003 11:59:15 AM

Ok, goldberg just did.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 17, 2003 11:59 AM
To: 'Petrie, Carolyn'
Subject: RE: GOT Trial Critiques and current protoco

YES
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Wednesday, September 17, 2003 11:58 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: FW: GOT Trial Critiques and current protoco

Shall I forward to Neil?

-----Original Message-----
From: Ronald N Goldberg [mailto:goldb008@mc.duke.edu]
Sent: Wednesday, September 17, 2003 11:56 AM
To: Petrie@rti.org
Subject: Re: GOT Trial Critiques and current protoco

---------- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 09/17/2003 11:56 AM ----------

Carmen M Hererra
09/17/2003 11:46 AM

To: Ronald N Goldberg/Pediatrics/mc/Duke@mc
cc:

Subject: Re: GOT Trial Critiques and current protoco

---------- Forwarded by Carmen M Hererra/Pediatrics/mc/Duke on 09/17/2003 09:53 AM ----------

Carmen M Hererra
09/16/2003 11:43 PM

To: Ronald N Goldberg/Pediatrics/mc/Duke
cc:

Subject: Re: GOT Trial Critiques and current protoco (Document link: Ronald N Goldberg)

Hi Ron,

The following are my major concerns regarding this protocol.
Attached are the rest of my comments (in blue) in reference to the specific questions.

- The main problem I see with with this protocol is not that it is complex, but that it attempts to study multiple management strategies at the same time. Given that the competing strategies are so varied and the confounders are many, the conclusions will likely be weak. For instance, the permissive approach, loosely defined as the acceptance of higher PaCO2s (PaCO2 > 65 with pH<7.20-7.25) and higher O2 (FiO2 > 50 to keep sats >90%) requirement before intervention will be compared to a "more conventional ventilatory approach". What is this? More conventional than what? What is "conventional"? Mechanical ventilation in itself is an important factor in the development of BPD. It is not possible to do this kind of study without clearly specifying what is the intervention , i.e. the "permissive approach" (whatever that might be, it needs to be defined by more than just CO2 values and include important determinants such as tidal volumes) and the control, ie. "conventional ventilation" (probably will need a survey to find out what ventilation strategies are currently being used). Not doing so risks repeating the experience of HFV vs conventional mechanical ventilation research, where most studies were criticized for not standardizing the control arm. Even if this study shows that CPAP + the "permissive approach" (as defined in the current protocol) is better than "conventional ventilation" (who knows what this means) + surfactant, this will not help clinicians to better care for their patients.

-- I would not electively extubate an ELBW infant with an active PDA or hemodynamically unstable, even if all the ventilatory/blood gases parameters were met as this protocol mandates:
Extubation Criteria for Intubated Infants in Treatment Group:
Attempt immediate extubation - within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation MUST BE attempted within 24 hours if all of the following criteria are met:
* PaCO2 < 65 torr with a pH > 7.20 - 7.25, (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 H2O, ventilator rate < 15 - 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
These criteria will continue in effect for 28 days from birth.

In fact, the evidence-based adult approach to extubation strongly supports minimal cardio-respiratory stability prior to attempting extubation (MacIntyre 2001). There is no such literature in babies, but the few studies that have looked into extubation protocols in children favor the same approach (Farias 2001). Why set up a high- risk fragile baby for failure knowing that it is very likely he/she will need reintubation at higher settings than prior to extubation (Veness-Mehan 1990)?

- I would strongly support protocol guided ventilator management such as that proposed by Durand: "optimizing lung inflation, avoiding both

atelectasis and overdistension, tolerating moderate hypercapnia, maintaining oxygen saturation within a narrow range, and aggressively weaning toward extubation" provided that the infant is hemodynamically stable. Durand showed that this was feasible: "the protocols for ventilator management of VLBW infants, both with HFOV and with SIMV were easily implemented and consistently followed" in 7 tertiary-level intensive care nurseries (Durand 2001). I believe a study design that incorporates a standardized approach to mechanical ventilation will result in much more meaningful conclusions.
Challenging? You bet!, but I think it is worth the effort.

Carmen

(See attached file: Response to Critiques of COT Protoco-CH revl.doc)

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu); M. D. Alan Jobe (Jobea0@chmcc.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. 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); 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); Georgia McDavid (Georgia.E.McDavid@uth.tmc.edu); Gerry Muran (ae5357@wayne.edu); Nancy Newman (nxs5@po.cwru.edu); RN Kathy Auten (auten002@mc.duke.edu); RN Nancy Peters (npeters@wfubmc.edu); Lucy Miller (lucmille@iupui.edu)
Cc:	M. D. Michael O"Shea (moshea@wfubmc.edu); Hastings, Betty J.; Petrie, Carolyn
Subject:	Reactions to COT trial from Wake Forest - with attachment
Date:	Wednesday, September 17, 2003 10:34:59 AM
Attachments:	cot trial-wfu.doc

To the Steering Committee regarding the proposed COT trial.

1) From Robert Dillard, Medical Director of NICU at Forsyth Medical Center where all deliveries occur:

"I've reviewed the above and believe there would be no significant problems associated with its implementation at Forsyth. The control arm for early CPAP would be virtually identical to our current practice. The treatment arm would be relatively easy to follow.

I'm thinking of suggesting that our SO2 range be 91-95% in the NICU, a range that's identical to the control range in the oxygen use part of the trial. I believe that using a lower range as done by Chow et al should only be implemented in a randomized trial with follow-up to determine safety. Once again, the COT study has the latter issue as a secondary item of interest.

In short, I'm in favor of our participating."

2) From Steve Block, Medical Director at Brenner Children's Hospital where all babies < 700 grams are transferred at 3-7 days of life:

"I think that this is a very compelling study! I particularly like the concept of a factorial design and getting at two birds, if not necessarily killing them.

From my experience with the VON DR CPAP study, which has some cross over, but is not by any means the same, there may be significant issues with designing a proper bubble CPAP device (such as the de Klerks have described) and training all participants in the use thereof. It is not certain that CPAP is the answer, or whether the way CPAP is delivered matters. The Fisher Paykel device has not been approved by the FDA. Is this study going to be used as part of their application? Is there going to be some sort of attempt at standardization of CPAP delivery?

In addition to Masimo there are other new generation pulse oximeters that are promising. Masimo has been studied best, but others may be as good. (Not Nellcor which is clearly inferior in neonatal and adult applications). Is Masimo going to support the study? Are other devices also candidates? Can sub studies be done that compare the reliability of competing new technologies?

I didn't have time to go into the study design and conduct in a lot of detail. But overall I am in favor."

3) From Candice Fike:

"I have looked at the early CPAP and Oxygenation trial and concur with the comments from the faculty at Rochester. The study design is way too complex and will make it extremely difficult to follow and even if followed well, it will be difficult to tease out any meaningful differences. Both notions being tested are extremely meritorious and I would favor separating them completely. I would do an early CPAP trial (and not allow use of the Neopuff in the conventional arm) and a separate Oxygen saturation trial. Furthermore, as to an oxygenation saturation trial, I think an additional arm should be added: use of low or high oxygen saturations as described until 32 weeks postconceptual age; but for those requiring oxygen after 32 weeks postconceptual age, some of the low oxygen saturation groups would now target high oxygen saturation (as in the recently published Australia study). In other words, it seems quite possible to me that we need to be targeting lower oxygen saturations in the first few weeks of life to prevent free radical damage, but that later on, for infants still requiring oxygen, it may be beneficial to target higher oxygen saturations, to improve total body growth and in particular, enhance lung vascular growth, and possibly have no adverse effect on CNS outcomes."

4) **From Cherrie Heller:**

"I finally got around to reviewing the COT protocol. I generally agree with most of the comments from Dr. Phelps. I was confused by the separate criteria for intubation for the two groups. I am also concerned that the mandated criteria for extubation of the treatment group does not take into account co-morbid conditions that might require continued intubation despite adquate oxygenation and ventilation (pre/post operative states, severe IVH, narcotic administration for pain control, etc).

One thing I do like about the study is that it would introduce Brenners and Forsyth to using the Neopuff. UNC uses this device and it has been a huge success (after a bit of griping). Of course, we would not need to be in the study to get the Neopuff.

Also, I like the idea of having some standard *guidelines* for intubation and extubation. Especially since, at least for the treatment group, the criteria proposed fit with my overall philosophy. However, I do prefer *guidelines* over *protocols* in terms of my clinical practice, but obviously for study purposes protocols must be adhered to as much as possible.
Overall, I think if they can simplify the protocol, perhaps using some of Dr. Phelps' suggestions that we should participate in the trial."

5) From NRN P.I.:

There seems to be a high level of agreement at our center, and at other Network centers, that the goals of the study are worthwhile. A substantial number of people expressed concern that the trial is not feasible because it is complex. By "complex", I believe they mean to say that: 1) a large number of clinical decisions related to respiratory care are prescribed by the protocol, providing many opportunities for protocol violations if these prescribed practices are not communicated well to the clinical staff and if reminders are not easily visible to clinical staff and 2) interpretation of the findings is not as straightforward. As we discuss this concern about complexity and feasibility, we should remember that we can distinguish ourselves from other networks if we can accomplish complex trials and that if we are able to execute the trial as it s designed, the trial will be more informative than a series of simpler trials.

A second concern expressed frequently is that withholding prophylactic surfactant from extremely premature infants exposes them to unnecessary risk. I am not as familiar with the evidence related to this issue, but I am reassured by Dr. Finer's equipoise related to this issue and the equipoise apparently held by the organizers of the VON trial, in which one group will not get prophylactic surfactant (as I understand the trail).

Implementation of this trial at Wake Forest will be extremely challenging, but I believe the efforts are well directed and I support the trial. I would request that additional efforts be directed at simplifying the protocol, but I am supportive of the factorial design and the combined treatment of (delivery room CPAP + higher thresholds for intubation/less restrictive thresholds for extubation) versus usual care.

From: Neil Finer
To: Seetha Shankaran M.D
Cc: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject: Re: GOT Trial Critiques and current protoco
Date: Tuesday, September 16, 2003 8:36:39 PM

Hi Seetha
Thanks for your input. We believe that the factorial is really a methodology to control the random variation in clinical practice, and the COT methodology replaces such random variation with balanced randomization. We all have SpO2 limits that we use and these differ site to site. In addition, our approaches to ventilatory support vary from the use of CPAP to prophylactic surfactant. The SpO2 arm will actually be transparent to the caretakers, and the ventilation methodology should be a choice of prophylactic surfactant and ventilation or CPAP and avoidance of ventilation.
As the sample sizes are the same for each question, we are making maximum use of our patients and getting as much information as possible, as well as learning whether these 2 approaches are complimentary.
We believe that an SpO2 of 85% is accepted by some units currently, and the data of Tin et al and Chow et al did not demonstrate increased mortality, although these were not prospective randomized designs.
We could certainly upward adjust the PaCO2 in the control infants.
We are trying to avoid intubation in the CPAP infants and forcing them to a higher FiO2 before surfactant, in the belief that early CPAP may be beneficial, and reduce the need for surfactant as seen at Columbia (Retrospective observations)
Thanks for your input. Talk to you tomorrow.
Neil

----- Original Message -----
From: Seetha Shankaran M.D
To: Neil Finer ; Langer, John C. ; Bhaskar, Brinda ; Hastings, Betty J. ; McClure, Beth ; Gard, Charlotte ; Kandefer, Sarah ; Das, Abhik ; npeters@wfubmc.edu ; auten002@mc.duke.edu ; nxs5@po.cwru.edu ; lucmille@iupui.edu ; ae5357@wayne.edu ; Georgia.E.McDavid@uth.tmc.edu ; ellen_hale@oz.ped.emory.edu ; grisbyca@email.uc.edu ; mbball@leland.stanford.edu ; ahensman@wihri.org ; cotte010@mc.duke.edu ; mcw3@po.cwru.edu ; martin.l.blakely@uth.tmc.edu ; vanmeurs@leland.stanford.edu ; BENJA005@onyx.dcri.duke.edu ; bvohr@wihri.org ; Brenda.H.Morris@uth.tmc.edu ; WOh@wihri.org ; 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 ; barbara_stoll@oz.ped.emory.edu ; aaf2@po.cwru.edu ; Jobea0@chmcc.org ; abbot.laptook@utsouthwestern.edu ; Poole, W. Kenneth ; higginsr@mail.nih.gov ; Petrie, Carolyn
Cc: Neil Finer ; Petrie, Carolyn ; Rosemary Higgins
Sent: Tuesday, September 16, 2003 2:05 PM
Subject: Re: GOT Trial Critiques and current protoco

Neil
At Wayne we discussed the DR-CPAP protocol and have the following comments

1) The overwhelming conclusion was that altho we all agreed that DR CPAP, 2 target ranges of oxygen saturations, aggressive versus non-aggressive weaning and permissive hypercarbia are all areas that need to be studied in an evidence based manner, the factorial design proposed would be very difficult to do. In fact you could study each of the issues by itself with sample size of 400 each successively and have much more "cleaner , straightforward" studies instead of a

single study with a factorial design and 1345 subjects

2) Primary hypothesis---would saturation of 85% be associated with a higher mortality?

3) We are all now practicing permissive hypercarbia---can we realistically intubate for only 50 torr in the "control " group?

4) It is not clear why surfactant dosing criteria are different in the 2 groups

We truly appreciate the monumental effort that has gone into this protocol
Hope this helps

Seetha

At 03:35 PM 9/14/03 -0700, Neil Finer wrote:

> Hello Everyone
> I know that we have a 2 hour meeting on Wednesday to discuss the COT Protocol. We have received significant suggestions etc and in order top facilitate a discussion I have prepared a response to all the questions asked.
> It is attached and I would ask that you bring it with you, as well as the revised protocol, also attached.
> I thank everyone for their responses, and look forward to a good discussion in DC.
> Carolyn, could you bring about 5 -6 extra copies of each to the meeting or more as you see fit for those who may not have been able to bring a copy.
> Travel well
> Neil

Seetha Shankaran, MD
Professor of Pediatrics
Director, Neonatal-Perinatal Medicine
Wayne State University School of Medicine
(313) 745-1436
sshankar@med.wayne.edu

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Cc:	Poole, W. Kenneth
Subject:	COT Conference call
Date:	Thursday, August 14, 2003 3:17:16 PM
Attachments:	COT study Aug 14 03.doc

Hello Everyone
I have attached a revised protocol with the major additions/changes in yellow. These reflect a restating of the sample size and estimates, Tables of outcomes for the various hypotheses (provided by Ken with thanks), and a preliminary change if we go to intubation for Surf for all.
I know that Shahnaz and others, me included, are concerned about intubating all for surf in the DR, but this may be the only acceptable methodology.
The original protocol still looks very acceptable to me, but I am somewhat prejudiced.
I have increased the PaCO2 to 65 torr and left the FiO2 at 50% for the treatment group for extubation.
Another thought - what if for the 26-27 week infants we use prophylaxis for surf for the controls and CPAP and a 30 minute look for surf. This group will be bigger and more likely to get away without surf, and have a higher percent that would never have had surf treatment? In most prophylactic studies about 40%-50% of infants required selective later treatment. Is this still too complicated?
Talk to you tomorrow.
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

July 3, 2003

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 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 natural surfactant, an intervention 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 precipitated by the 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 where performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges 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 demonstrated that the early use of CPAP 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]. The use of early CPAP also appears to decrease the need for subsequent surfactant use and mechanical ventilation in premature infants. 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.[6]

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 recommended 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 new technology that can be used to tightly control 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 recommended levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels will 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 [7]. The use of early PEEP improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [8,9]

1.4 Human Experience: Ventilatory Support

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 infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP soon after delivery[10]. 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[11]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[12] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that early use of CPAP was associated with 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.

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.[13] 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[14]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages.

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[15]. 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[16]. 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.[17] 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)[18]. 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[19] 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[20], 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.[21] 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.[22] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[23]

There are currently no studies which have prospectively compared early 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.[24]

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.[25] 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.[262728] 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.[29] 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.[30]

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.[31 32] 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.[33] 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))[34]. 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).[35] 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%).[36] 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 < 1000gm, there was a decrease in the incidence of ROP.[37] 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.[38] A subsequent trial conducted in Australia that compared SpO2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or neurodevelopmental outcome, but resulted in increased duration of oxygen supplementation.[39]

More recently 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.[40] 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.

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.[41] 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[42] 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 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 (≤ 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.

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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.

3). We hypothesize that the that relative to infants managed with surfactant and CMV and a high SpO2 range that the combination of early CPAP and a permissive ventilator strategy with a lower SpO2 range will individually and collectively positively impact the NDI/Mortality

outcome at 18-22 months corrected age.

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 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 threshold 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 to 27 completed weeks (up to 27 6/7th) 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. 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

Strata: There will be 2 randomization strata, infants of 24 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) and to either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent following admission, 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 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

The randomization to either a high or low SpO2 will be performed immediately following NICU admission, with a maximum allowable delay of 1 hour following NICU admission.

TREATMENT Group

Early CPAP – Treatment Group - Both Strata - 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 and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 7– 8 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.

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 receive intubation for resuscitation in the Treatment group may 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 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress..[434445] 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.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20 or nasal SIMV.

All non-intubated Treatment infants will be evaluated at 30 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 $\geq$ 90%, they will be immediately intubated and given surfactant. For infants who appear unstable, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SpO2 $\geq$ 90%

OR

All Treatment infants will be intubated in the DR following usual resuscitation practices and be given surfactant within 15 minutes of delivery, and then transferred to the NICU, receiving PPV. Infants of 26-27 weeks who are stable on room air by 10 minutes of life do not require intubation for surfactant treatment

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 ±2 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants (Only 26-27 week infant who were on RA by 10 minutes): ***These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCOs and require higher FiO2 before intervention***

Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 ≥ 88% (using the altered Pulse Oximeters)
- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20,
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

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.

<u>CONTROL Group</u>

<u>NOTE: 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 30 minutes provides a significant survival benefit</u>

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 in the delivery room.

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant if requiring any supplemental Oxygen by 30 minutes.

Intubation Criteria for non-intubated Control infants > 30 minutes of age in 26-27 weeks strata: These Control infants ***MUST*** be intubated and receive surfactant if they meet ***ANY*** of the following criteria:

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 88
- The use of CPAP
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (**Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1**)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 the centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Current Protocol for ensures an evidence based intervention with prophylactic surfactant for all enrolled infants apart from those who are stable on RA at 10 minutes after birth, and requires intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of MAY be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

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 POs 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. 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%.

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 as of June 27th 2003, that this technology is workable.

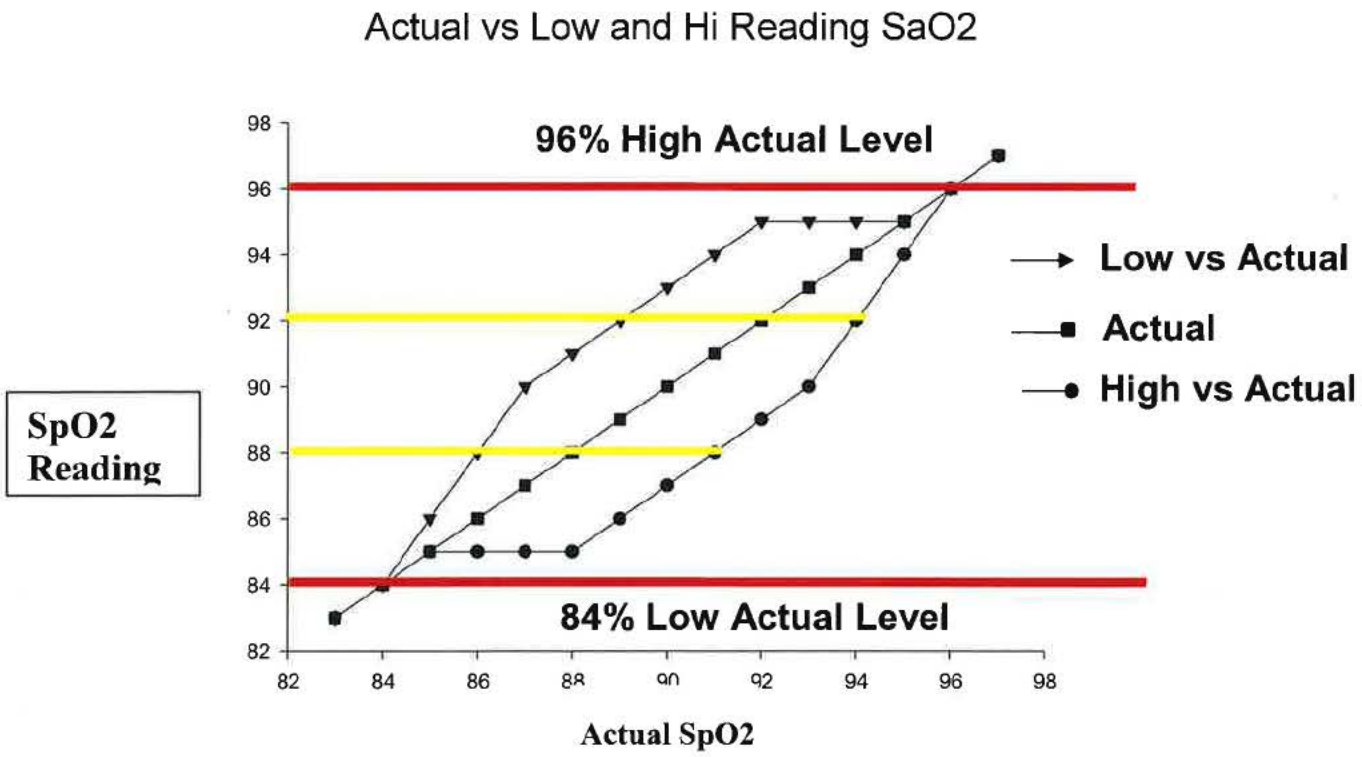
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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 96%. This will provide for an overall set of limits on actual SpO2 of 84% to 97% 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 96%. 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. 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 the PO SpO2 data was used in the DR CPAP Pilot trial

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.[464748]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants.

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)[49]
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

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP; and 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.

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 DRCPAP (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

DRCPAP	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 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

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

8 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

9 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

10 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.

11 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

12 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

13 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

14 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.

15 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.

16 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.

17 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.

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

19 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.

20 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

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

22 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.

23 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.

24 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.

25 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;

26 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

27 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

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

29 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

30 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

31 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

32 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

33 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

34 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

35 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

36 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.

37 Flynn JT; Bancalari E; Snyder ES; Goldberg RN; Feuer W, and Cassady . A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326

38 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

39 Askie,LA, Henderson-Smart,DJ, Irwig,L, Simpson, JM The Effect of Differing Oxygen Saturation Targeting Ranges on Long Term Growth and Development of Extremely Preterm, Oxygen Dependent Infants: The Boost Trial. .Pediatr Research 2002;45;348A

40 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

41 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

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

43 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

44 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

45 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

46 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

47 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 .

48 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

49 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: Wally Carlo, M.D.; Shahnaz Duara; Ed Donovan; "avroy fanaroff"
Cc: Higgins, Rosemary (NIH/NICHD); Neil Finer
Subject: COT Meeting tomorrow
Date: Tuesday, September 16, 2003 7:33:38 PM
Attachments: Response to Critiques of COT Protocol Revision for Vent Group only.doc

---

Hi Everyone
Thanks for a very productive call. Your support and enthusiasm was impressive.
I have modified the responses to the critiques highlighting some of the issues that we discussed today.
I put the important issues at the top, and I hope that this will help in tomorrow's discussion
To review our strategy:
I will provide an overview and how we got here. I will briefly discuss the factorial, the ventilation and SpO2 arms, our philosophy of not overprescribing interventions and the idea that we are challenging 2 philosophies of care in the vent arm. I will thank everyone for their thoughtful input, and indicate that we have had a good response, and many useful ideas which have resulted in protocol changes. I will emphasize that we remain flexible, and committed, and have given substantial thought to having further site discussions regarding implementation.
Each of you will discuss site specific issues, details of the weaning protocol, how detailed (Shahnaz), the approach and rules/protocol versus guidelines and the actual equipoise that exists (Ed), the requirement for the Coordinator to ensure protocol compliance (Wally).
I will discuss the input from Masimo, and the SpO2 design, and our plan to do a feasibility to prove the reliability and accuracy of the POs and a bit about the Bubbleflow if it has not already been raised.
Major discussions:
Factorial design - We are replacing a random variation with a balanced randomization. Wally and Neil
Use of lower versus higher SpO2 ranges - Shahnaz
Protocol complexity, details and implementation at sites - Ed
Ventilation arms Prophylactic Surf vs CPAP - Neil, Wally
Sleep well
Neil

Response to Critiques of COT Protocol: Sept 14, 2003

Q.The factorial design of the trial was concerning because of two separate primary outcomes. The rationale for linking the two studies was unclear. Also the potential for having interactive effects which could not be quantified was concerning, particularly if those effects might mask a potential benefit of one of the interventions. If there is scientific rationale to look at the effect of DR CPAP/permissive ventilation and SpO2 ranges on death/BPD, that would make the case for the factorial design much stronger in our view.
There is a high chance that the study could be stopped early for one reason, to the detriment of the factorial designed second question.

A.**We have discussed this issue with Ken and we believe that while this is a factorial by design, we are essentially prospectively enrolling infants into 2 simultaneous randomized trials, the interventions of which they would receive anyway in a non-random fashion. Note that the Network does not practice prophylactic surfactant, and there is little agreement about acceptable SpO2 ranges between centers. We will be able to evaluate additive effects, and if an interaction is powerful enough, we will clearly recognize it. Since we currently combine in some way these clinical approaches, addressing them through a clinical trial will result in balanced patient allocations to each of the 4 cells. We are replacing a random variation with a balanced randomization. The Network is somewhat concerned regarding the SAVE trial, but there is currently little if any evidence to suggest that any arm of this trial would be harmful. Indeed. There is potential benefit to each arm if one believes the current evidence in that prophylactic surfactant is an evidence based intervention, and higher SpO2 may decrease or increase severity of ROP (STOP-ROP, Tin et al), while lower SpO2 may decrease BPD (BOOST, STOP-ROP), and there is substantial interest and preliminary data supporting early CPAP.**

Q.The feasibility of the study was a great concern for a number of reasons including the complexity of study design, the difficulties of obtaining consent for such a complex trial from women in extremely preterm labor, and the problems of identifying and enrolling study candidates at all hours (even though we have in house fellows or faculty every night).
This is of greatest concern with infants at 24 weeks gestation and the need to in essence know if an infant will be given "full resuscitation" prior to delivery (in order to randomize and have every thing prepared prior to delivery). For right or wrong, we do triage many infants at 24 weeks gestation and the determination to resuscitate is determined by the provider at the time of birth. In addition, it is very difficult to envision discussions with mothers about the issue of viability/use of resuscitation at this gestation, and simultaneously explaining a study of the scope and magnitude of COT. We cannot reconcile obtaining consent before delivery for a fetus that in our hospital may not be given care. The question of intention to treat, and what happens to an infant who has been consented, randomized, and then at delivery is not supported has not been

answered. A related consent issue is the mother who comes to L & D and rapidly progresses to delivery before she can be consented. It is difficult to estimate the number of women who fulfill such criteria, but use of a waiver may help for this sub-group of study candidates.

A. We believe that this study is complex but doable by the Network. We have experience with pre-delivery consent and found that it worked well for the DR CPAP such that waiver was infrequently required (13/104). This population is usually consulted by Neonatology prior to delivery and we would use this opportunity to discuss the protocol and obtain consent.
The DR CPAP used a randomization by site by week which facilitated the randomization, but led to an imbalance. This would also require a separate randomization for the pulse oximeter, but that could be done by a phone call or envelope or pre-labeled POs. We can certainly discuss whether there is support for such a methodology, which would not separately randomize by strata, if it were to be kept simple. In addition this methodology does not allow for concealed randomization, but the use of envelopes or any other method still allows some time before the intervention where the team is aware of the selected approach. Using a site by week or day etc methodology also randomizes infants of multiple pregnancies to the same arm, which may be appealing to parents. In addition it is much less stressful for the resuscitation teams who would essentially approach all infants on their watch the same way. If we used a daily schedule, we would suggest that shift change in the morning would be the logical time to institute the next allocation.
We would anticipate using double sealed envelopes that would indicate the randomization to either Control/Prophylactic Surf or Treatment/CPAP and a second code indicating the number of the Pulse Oximeter to be applied within an hour of birth. The center would be supplied with a number of POs with unique identifying numbers. The teams would be asked to have surfactant available for all such deliveries, as Treatment infants who require intubation for resuscitation will also receive surfactant in the DR. The delivery room interventions are very straightforward – All Control infants apart from those who appear stable < 30% in the 26-27 week strata are intubated for surfactant and taken to the NICU for continued ventilation and weaning. All Treatment infants receive CPAP/PEEP and may only receive surfactant in the DR if intubated for resuscitation. From DR CPAP we would anticipate that about 50% of the 24-25 week strata will be intubated in the DR and they will receive surfactant at that time. We are then providing an early window to give surfactant to the Treatment infants to provide them with the added benefit of this intervention. It should be noted that for DR CPAP which also enrolled at all hours, that the coordinators were usually not in the DR.

Q.Inadequate standardization of mechanical ventilation. I think this is a major flaw of this study protocol. One of the primary hypothesis is that CPAP + "a permissive ventilatory strategy" (poorly defined by CO2 levels) begun in the DR compared to conventional mechanical ventilation (not

defined at all)+surfactant will result in an increased survival w/o BPD at 36 weeks. Mechanical ventilation itself is a factor in the development of BPD. Ideally, the objective should be to show that early CPAP+ optimal mechanical ventilation (if needed) compared to optimal mechanical ventilation + surfactant increases survival w/o BPD. There are no suggested ventilator management protocols, no mention of tidal volumes, a known important determinant of lung injury, or synchronization (known to be associated with shorter duration of mechanical ventilation in babies). The fact that the interventions cannot be blinded (for obvious reasons), makes it even more important to have a standardized mechanical ventilation protocol to avoid bias. This would greatly strengthen the study conclusions.

*A.***We have tried to keep the ventilator management as simple as possible and allow centers to continue their current practice.**
This study will involve comparing 2 philosophies of care, and will require a supportive attitude at all sites by individuals who have equipoise, the establishment of a few rules and some guidelines, and a prospective plan for education at each site. We have discussed the potential benefit of site visits, and other educational approaches including video in-services etc.

Q.The highest rated design option was to eliminate the delivery room component (allowing faculty to routinely use both CPAP and prophylactic surfactant and to enroll infants after NICU admission) and use a factorial design to simultaneously assess
conventional vs. permissive (conservative) ventilation (with different criteria for intubation and extubation)
conventional vs. conservative saturation goals
Q.Conduct a 3 armed ventilation trial (adding group given DR CPAP + prophylactic surfactant) and eliminate the evaluation of different oxygenation saturation goals. This was the 1st choice of one faculty member and the 2nd choice of 3 faculty members, though they were aware such a trial was in process outside the Network (but would probably not resolve the issue).

A. **The DR CPAP feasibility trial demonstrated that we could do a trial of ELBW infants with an intervention in the DR with few protocol violations. That trial was a preliminary evaluation that demonstrated that 23 week infants all required intubation at delivery, and that it was possible to have resuscitation teams adapt to a new resuscitation approach and device. The current trial design grew out of that experience and is consistent with the charge given to the ventilation group to develop a trial that would test the value of early CPAP compared with a more conventional approach.**
This design suggests that CPAP plus surfactant in the DR is the best approach, but this approach has never been tested by anyone. There is a belief that these may be

equivalent interventions, as noted above. In addition, we would be selecting an approach used by almost no one in the Network, to our knowledge. Centers that use early CPAP tend to delay intubation for surfactant, and centers that intubate in the DR, may not be using CPAP, and if they did, would only be using it for the time prior to intubation. The DR CPAP study demonstrated that we could enroll infants and do a randomized intervention in this environment. VON is pursuing such a methodology, and we wish them luck. Our trial is complex enough, novel, and will address different issues so as to be complimentary to the VON efforts.

Q.With respect to the design, multiple faculty members had major reservations about foregoing prophylactic surfactant, particularly when the trial's current design would not allow a determination of whether CPAP/PEEP administered in the absence of prophylactic surfactant produces outcomes worse than CPAP/PEEP administered with prophylactic surfactant.
Q.Early surfactant administration. I'm not totally comfortable delaying this intervention. Available data supports prophylactic use of surfactant; the earliest, the better. It's my clinical impression that since we started the surfactant administration in the DR because of the iNO protocol, kids have less severe initial respiratory disease and require less mechanical ventilatory support. In addition, there will be a conflict with the early administration of surfactant for the iNO protocol in kids assigned to the treatment group (early CPAP).
Q.Given the evidence of the benefit of prophylactic surfactant, the complexity of the current design, the likely length of the study, and the high likelihood of protocol violations I would not favor the trial as currently designed.

A. **Our study is designed to answer the question of whether the use of early CPAP/PEEP followed by a restrictive approach will produce respiratory outcomes equivalent or better than prophylactic surfactant with a more conventional strategy. The VON trial will have 3 arms, one of which will be early Surf with extubation etc. We believe that the question that we have asked is as important as the question being posed, and we cannot ask every question in this trial. In addition, the Network does not currently uniformly provide prophylactic surfactant, and thus this trial may benefit any enrolled infant. The practitioners of early CPAP believe that the use of early CPAP is as effective as surfactant, and this is borne out by the decreased use of surfactant at Columbia compared with Boston centers (Van Marter 2000), and a lower BPD rate.**

Q"*control infants should all be intubated in the DR and receive surfactant within 15 minutes; forced extubation to NCPAP or NSIMV should not be permitted. We felt that such a design would permit the needed evaluation of DR-CPAP with prophylactic surfactant*"

A. **We agree and this is the design with the exception that those not requiring > 30% Oxygen or CPAP by10-15 minutes could avoid intubation.**

Q.The use of delivery room surfactant for the control group strata of 24-25 weeks represents a major practice change. There is concern regarding a long learning curve, working through the logistics of getting the surfactant to the delivery room, and the drain of resources on the NICU by the longer period of time and the additional personnel needed in the delivery room. Furthermore, in a delivery service that has on average 40 deliveries per day (and has had up to 87 in one day!!!), the issues of communication between Obstetrics and the NICU is not to be underestimated. The latter represents areas where we have limited control, and thus may limit our success of a major change in practice in the delivery room. We have been attempting (with good success) to provide early rescue surfactant and administer surfactant in the first hour of life. If we were to combine a NICU/prophylaxis approach without using a CXR, we are pretty confident that surfactant could be given within 30-40 min following birth

A.**This nicely presents the balance within the Network of the use or lack thereof of DR prophylactic surfactant. Wow!! This place could do the study by themselves!! We had many discussions about the relative benefits of prophylactic and early surfactant, and they have never been really tested against each other. Both are good, and most assume that prophylaxis is better, but many studies were pre antenatal steroids, and some were pseudo-randomized, so we probably do not have the final answer. In addition, prophylaxis overtreats with 40-60% of the infants who may not have reached rescue criteria, depending on the criteria. Early is usually less than 2 hours, selective was somewhere between 6 and 24 hours, and the references to the Cochrane data is shown.**(Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software)

Q..*In assessing oxygen saturation goals, it was agreed that this is question of central importance but that the study would be meaningful only if there was great effort to regulate FiO2 and adhere to saturation goals.*

A.**We partially agree, and believe that even if a great effort is not made, the groups will have significantly different SpO2 ranges, which may lead to significant outcome differences.**

Q.The need to define surfactant re-dosing criteria.
Is there any restriction on what kind of surfactant can be used

A.The **following has been added to indicate "**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.

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

Q.The need to initiate caffeine therapy early in the infants in the treatment arm

A.**Agreed and we have added the following**

"**Use of Caffeine**:

Caffeine may (should?) be administered 2 hours prior to planned extubation, and for any clinically significant apnea.

Q.The need to obtain consent prior to delivery for study patients and to randomize only those infants whose mothers had received at least one dose of antenatal steroids prior to delivery.

A.**This has not been addressed and we are unclear whether this should be done. All infants are at risk for CLD and ROP< these infants even more so. Why should they be denied entry? Randomization should create an equal number of such infants, and no study to date regarding surfactant or post natal steroids and no Network study to our knowledge has use such a methodology.**

Q.Many faculty felt that one of the most important questions is still the role of bubble CPAP

A.**We agree and would like to use the Bubbleflow. We are discussing with Fisher&Paykel this possibility, and we may have to file an IDE. They are trying to satisfy the FDA at present, and it is conceivable that they will have 5-10K approval in the next 2-3 months. If not, we could file an IDE and provide some of the needed evidence that they would require for FDA approval. There is recent data that suggests that bubble CPAP offers no advantages or disadvantages to gas exchange (Morley et al PAS, 2003) We would encourage the use of a single system at eacg center**

Q.*Some faculty questioned the need for different intubation and extubation criteria*
the criteria for intubation (CO2 65 and extubation CO2 60) are hard to reconcile

A.**We are trying to maintain a significant difference between the ventilation management protocol and use stricter criteria for the Treatment infants. There were inconsistencies in the PaCO2 and SpO2 criteria that we have removed, and now the intubation and extubation criteria are similar within a**

group. We have specified actual criteria to ensure such differences. One issue not previously addressed was unplanned extubation in the Control infants and we have now added the following

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 intubation criteria, apart from the need for CPAP, for more than 4 hours, intubation should be performed.

Q.*Extubation criteria for intubated control group infants. According to the protocol extubation may be attempted if all the criteria are met. Knowing all the risks and complications associated with mechanical ventilation, I think is unethical to keep a baby intubated just because the CO2 level is over 50.*

A. **The Control infants criteria for extubation was felt to represent a proximation of current conservative practice. We wanted to keep a spread between the Control and Treatment infants. We would be happy to consider a broader range, ie up to 55 torr. This should be discussed.**

Q.Some faculty raised the issue that intubation/extubation criteria would change with the masked high and low sats and were concerned that this could affect the duration of ventilation or the timing of intubation.

A.**We believe that the use of the Study SpO2 ranges would effect decisions by only a 3-4% noted SpO2 difference and that there is currently a wide range of acceptable SpO2 and PaO2 that are utilized throughout the Network. We do not believe that the use of the study Pos with altered ranges will effect clinical decisions to a major degree, and the knowledge that values below 85% and above 95% are real will ensure that for these deviations all staff will know the real SpO2 value.**

Q.It was strongly suggested that the COT committee consider dropping the oxygenation part of the study and concentrate on the CPAP component of the trial. Keep in mind that the Network feasibility study was for the CPAP trial alone. Also the experience from STOPROP trial should be reviewed to see whether the oxygenation component of the protocol is doable or not

A.**As previously explained we currently vary the acceptable SpO2 between centers, and there is preliminary data that lower SpO2 may be better (Tin et al, Chow et al). Both STOP ROP ands BOOST studied infants > 32 weeks PCA or at pre-threshold (about 34 weeks PCA) and no study has prospectively evaluated early ranges of PaO2. With the blinding, we believe that this portion of the study is much easier than the ventilation intervention.**

Q.How do we handle multiple gestations? Exclude, enroll all fetuses, enroll only one, if so which one

A.**Frequently asked. In response we ask whether any Network study has enrolled multiples as a unit. We would prefer randomization of multiples to the same arm, and we will ask RTI to discuss the feasibility of this approach. We are comfortable with either method, and parents would probably prefer unit randomization, but that may introduce imbalance. This study should follow the general approach being taken for all current trials such as phototherapy which randomizes all multiples separately.**

Q.How about dropping 24 and 25 weekers and expand gestation strata to 28 weeks. In other word, change inclusion criteria to 26/0 to 28 completed weeks.

A.**The group at greatest risk and least well studied is the younger strata. We may be the only group willing to evaluate this group.**

Q.Concerns were expressed regarding the permissive ventilation strategy. Is pH >7.20 for extubation realistic. It maybe better to give a range of perhaps, 7.20 – 7.25 to allow for some flexibility.

A.**Done, and to demonstrate the differences in the Network between sites I have added a response from Cincinnatti**
"For study purposes, it is OK to wait for severe apnea or pH < 7.2 and pCO2 > 60 and fiO2 > 0.5 to intubate infants 24-28 weeks. 10 Yes 0 No 1 ?"

Q.Same applies to the rate of ventilator for extubation in the treatment group. Rather than < 15, use a range of 15-20

A.**Done**
Q.*A couple of faculty members expressed serious concern about high O2 range of up to 95%. They would be willing to go along with 92 0r 93 % . It was pointed out that a paper in this week New England Journal showed better outcome in regards to oxygenation target at 91-94 % as compared to 95-98%. Should we consider dropping the range to 90-93, not 90-95% ?*

A. **As discussed by Dale, the BOOST trial started at 32 weeks PCA, and the ranges chosen are somewhat arbitrary. There are no previous data to use for any chosen range and so we have tried to choose different ranges within the 85% to 95% range, based on previous data. We believe that most sites will want larger rather than narrower ranges for alarms and thus we are aiming to have significant differences within the 85% to 95% range.**

Q.Altered pulse oximeters. I would rather know the "real" saturations. There are delays and inaccurate values with the use of current oximeters as they are. I don't like the idea of adding even more room for error by masking the devices.

A. ***There is currently some offset in the relationship between actual SaPO2 and SpO2. Our scheme would alter the PO reading only between 85% to 95%, and by a maximum of 3%. This level of error is mimimal and as most units do not actually measure SaO2 but assume a value, which is based on adult hemoglobin values, the actual values of SpO2 are used for monitoring and trends. If there is a concern about the actual PaO2 a blood gas and/or a TcPo2 device can be added. We are confident that the use of such will not result in unblinding. In addition the BOOST trial altered the ranges by 2% throughout the entire range, and never read the actual SaO2 values.***

Q.It was also suggested that the COT Committee performs a survey for current practice in regards to the intubation and extubation criteria and practices among centers with the goal of setting up criteria that are as close to current practice as possible.

A.**We will loosely poll at the Steering Committee meeting. If further information is deemed helpful, it can be obtained. We are probably recommending criteria that do not exactly match any center's current practice, and that applies particularly to the Subcommittee members. These criteria are thought to represent a reasonable consensus, and maintain separation between the groups.**

Q.The most consistent concern was a lack of standardization of modalities of therapy, and with acknowledgement of different delivery systems having different levels of effectiveness, the Network should strongly consider standardization of the CPAP device.

A.**We will attempt to obtain the Bubbleflow for this trial as noted above. Attempting to use another apparatus for standardization would be expensive, and without any evidence basis.**

Q.The group also voiced concern over the perceived 3 different aspects of management to be investigated in one trial; early CPAP vs intubation early, permissive vs more aggressive ventilation, and the factorial design for O2.

A.**This is a complex trial, and the CPAP and permissive approach are part of a single strategy, much modified to be acceptable within the ranges of current Network strategies. This will be compared to prophylactic**

surfactant and a more conventional ventilatory approach. The longer we delay, the greater will be the drift toward a more permissive approach by all centers without adequate evidence.

Q.With ongoing study in Benchmarking, there may be significant management practices that he committee may want to standardize for the study. We believe that failure to standardize "Benchmarking" findings or best care will obscure the results as mechanical ventilation and early NCPAP are only part of the multifactorial etiology of BPD.

A.**By the initiation of this trial, benchmarking will be close to completion. We have tried to suggest a minimal of standardized approaches, and indeed are testing the comparability of prophylactic surfactant to early CPAP. The Network has been aware that prophylactic surfactant is an evidence based intervention, but this approach is not standardized within the Network. This study will force such an approach for the Control infants, and the results will aid in determining future best practice. There is no currently accepted standard care regarding SpO2 limits.**

Q.Nasal CPAP delivered by high flow nasal cannulae is not considered but has become standard practice in many nurseries.

A.**Nasal Cannula may deliver CPAP but it is unregulated and unmeasured, and we are not prohibiting its use for infants subsequent to the discontinuation of CPAP. We would not, however encourage its use till better studied.**

Q. CPAP level. Columbia is the US center with most CPAP experience and very low BPD incidence. They have used a level of 5-6 cmH2O for 30 years (they also use mouth straps- to keep the mouth closed- though). We do not use a level of 7-8 cmH2O on a routine basis and I have not seen any published data about this level of CPAP support. To my knowledge, Dr Morley's data (cited in the protocol) has not been published yet (ie. peer reviewed). I have concerns about risks for airleaks and abdominal distention (interfering with feedings) if we used these higher CPAP levels.

A. **We are aware of some animal data that 7-8 may be superior, but we have changed the protocol to 5-6 cm H2O.**

Q.Ventilator rate < 15 bpm as extubation criteria. We rarely have babies with SIMV rates less than 15 bpm in our unit. Research data shows that rates <20 bpm significantly increase the work of breathing and oxygen cost of breathing. I worry about decreasing the rate to less than 15 bpm in kids who already are using low PIP (equivalent to breathing through a high resistance straw, ie. 2.5 ETT, most of the time) just to meet these

extubation criteria as this would increase the risk of atelectasis, respiratory fatigue, and extubation failure.

A. **We have expanded the extubation range to 15 – 20 bpm**

- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 15 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

Q.Concern was raised about the intubation criterion of an FiO2 0.50 to maintain an SpO2 ≥ 88%. We would not know this because the limits on the pulse ox for the low range is 85-89%.

A.**We have standardized this criterion to a SpO2 > 90%, the midrange of the SpO2 target range for both groups, and thus the Actual SpO2 could be 87% or 93% approximately. There is some information that currently SpO2 values may be somewhat optimistic, and all caretakers will be aware if the actual SpO2 if the true SpO2 is < 85% or > 95%. This study is designed to determine if such lower limits are beneficial as suggested by Tin et al and Chow et al.**

Q.Page 12 – The injunction that "extubation must be attempted within 12 ± 2 hours . . . would be difficult if your clinical judgment dictates otherwise. For instance, extubation criteria are met but the child has a ductus, is developing pulmonary edema and therefore at risk for pulmonary hemorrhage.

A.**We have changed this to a 24 hour period to allow more flexibility, and not force extubation, and re-intubation may delayed for up to 48 hrs**

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 24 hours if all of the following criteria are met:***

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. ***The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.***

Q.Permissive ventilation adds another confounder into the study and may cloud the outcome. It is another approach that needs to be validated. This may be further exacerbated by statements like "the minimum" criteria proposed on page 13 (i.e., intubation may be delayed according to clinical preference).

A.**The Network would agree that permissive hypercapnia needs further testing. The SAVE trial was an attempt and the COT trial would provide adequate power to answer this question. The treatment group is intended to allow less intubation and less exposure to ventilation and determine if this approach is effective in reducing BPD.**

Q.Protocol violations will be extremely common. Particularly night crews changing ventilation
Concern was raised about the time and monitoring of such a complex study to assure that compliance is high. The results of the feasibility trial (re: compliance) were not convincing given the limited time and intervention relative to the COT trial. There will need to be a hard look at what is needed in terms of Network Coordinator/PI time to realistically facilitate this study. The level of interaction that may be necessary between study personnel and attending staff is such that there may be negative spill-over to other Network endeavors (the latte is my personal concern).

A.**We believe that the current iteration is somewhat simpler, and that additional surveillance may be required as suggested from Alabama "There is concern about the need to monitor compliance and the agreement is that there will be a need to have a research coordinator assess protocol compliance twice daily with twice daily feedback (at least initially) to the caretakers (and PI/designated opinion leader as needed). This should be budgeted into the capitation".**

Q.Allowing use of the Neopuff in the control group will reduce the potential differenced between the groups, making the testing of CPAP/EEP in the DR invalid

A. **We hope that most of the control infants will be intubated in the DR for surfactant and the continuing use of CPAP in such infants will constitute a criteria for intubation. Therefore the use of the Neopuff would not confuse this trial. The Treatment infants will not be intubated in the DR except for resuscitation intervention. In addition, this trial is to evaluate a total approach involving early CPAP and a continuing permissive approach, not just the use of CPAP/PEEP in the DR. Even the DR CPAP feasibility trial was not powered to evaluate the benefit of DR CPAP.**

Q.What will you do about kids who need to have upper and lower saturations looking for shunting?

A.**Do what you normally do which is to drive the SpO2 > 96-98% and look for pre vs Postductal shunting. We will ensure that for such purposes and second identically altered PO will be available for such an evaluation. Any**

pre- vs post ductal difference will be noted, and all values > 95% are actual.

Q.Can you randomize an infant into the oxygen study if he is missed consent for the DR management portion of the trial? (or if the parents refuse that part?)

A.**Not with the current design.**

Q.You need some criteria to allow for intubation for some degree of excessive work of breathing

A.**What is the data to support this request? We believe that we need to use objective criteria as are listed. Clinicians will make the ultimate decision, and we may have to analyze how often this happens.**

Q.What if you don't have arterial gases? how do you use PaCO2 values? pH ? use VBG or CBG?

A.**In the absence of an arterial line, a capillary sample is preferred, but venous values may be used, and should be interpreted as reading 5 torr higher than the arterial PaCO2. This has been added to the protocol**

Q.In addition to Masimo there are other new generation pulse oximeters that are promising. Masimo has been studied best, but others may be as good. (Not Nellcor which is clearly inferior in neonatal and adult applications). Is Masimo going to support the study? Are other devices also candidates? Can sub studies be done that compare the reliability of competing new technologies?

A. **We believe that Masimo has the best technology. More importantly however, they are willing to do the modifications to the pulse oximeter to allow blinding, as well as alter the ranges, while providing real values < 85% and > 95%. They are small single product company, whose CEO is committed to improving care. They will charge us cost on the monitors, and are not charging for the modifications, and will then alter the software after the trial to allow the sites to keep the POs. The Masimo new generation device works very well, and is very readable. I do not believe that we would get as good a product or support from any other company. NO I have no shares of Masimo, I am not a paid consultant, but they have provided us with POs for testing, and we are working with them to change their software to make their devices more appropriate in certain situations. They did buy me lunch once at Baja Fresh.**

QTarget range of pulse oximeters: Although the range of 88-92% is ideal, it may be quite difficult for nurses to keep infants in such a tight, narrow range. Although the boost trial

may be cited, the infants in the COT study will have a younger post-natal age and will be studied during their acute illness and the evolution of BPD when they are more labile. For the sanity of the nurses, the range needs to be broader, say 87-93%.

A. **We need to discuss the alarm ranges, and these remain flexible. IF the teams aim for the center of the range, we think that we will achieve a true separation. WE would test the PO in the5 DR CPAP centers before they are ready for distribution.**

Q.Surfactant: Will the cost of additional surfactant use for prophylaxis be covered by the study? There are tremendous financial pressures at this point in time.

A. This has not been planned – 80% of the infants being studied already receive surfactant, and we believe that the use will fall, as many Treatment infants will not receive, and this may balance the prophylactic use in the Control arm.

Q.SaO2 criteria: For all of the extubation and intubation criteria, a SaO2 of >90% is listed. However, by one hour of age, the infants should be on the study pulse oximeters with a target range of 88-92%. This could be a source of confusion.

A.We have chosen the midrange of the SpO2 range as a reference for such decisions and do not believe that this would be a problem, as it will be only 3% different than actual.

Q.Neopuff: What is the status of the Neopuff with regards to FDA approval?

A. **The Neopuff is FDA approved.**

From:	Neil Finer
To:	Poole, W. Kenneth
Cc:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD); jobea0@chmcc.org
Subject:	COT Trial
Date:	Tuesday, September 16, 2003 7:12:40 PM

Hi Ken
I hope that you get to read this before our Steering Committee COT meeting tomorrow at 2:30 PM Eastern Time
Our group is trying to plan for all contingencies and thus we would ask you to consider the following scenarios
If the Steering Committee votes down the COT Trial:
We will then propose the following - That those centers interested in the Ventilation arm only indicate their willingness to conduct that trial, that centers willing to do the SpO2 trial so indicate, and that those willing to do the full factorial indicate that.
We would like you to think about these possibilities and the number of sites/patients and the feasibility of this approach. We know that the sample size is essentially the same for either arm alone and thus the sample size is known. We also know the Network numbers and site numbers. Could you look at the numbers of infants per site in the 24-276/7 wks and then potentially have a calculation assuming that 50% or 70% of eligible infants were enrolled from these (use the current % of eligible from phototherapy). We could then determine if any or all subgroups, if it comes to this, would have power, or which one(s) would have adequate power. There is not a lot on the Network menu, and we are going to do our best to convince the group that the current version is doable.
I hope that we do not need you to provide this information, but I thank you in advance for preparing such a response.

Neil

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: GOT Trial Critiques and current protocol
Date: Monday, September 15, 2003 7:27:54 PM

Rose: Good. Talk with you soon. wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 15, 2003 6:20 PM
To: Wally Carlo, M.D.
Cc: 'Jobe Alan (E-mail) '
Subject: RE: GOT Trial Critiques and current protocol

WALLY
We will set up conference calls by the end of tomorrow to acomplish most of the work that was orginally scheduled for the steering committee meeting. Details will follow.

Rose

-----Original Message-----
From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD)
Cc: Jobe Alan (E-mail)
Sent: 9/15/2003 6:15 PM
Subject: RE: GOT Trial Critiques and current protocol

Rose: This is a great excersise but I am concerned that we do not delay protocols. We are a bit stagnant and do not have protocols in the pipeline. Wally

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 15, 2003 7:41 AM
To: Abbot Laptook (E-mail); Wally Carlo, M.D.; Dale Phelps; Ed Donovan; Ehrenkranz Richard (E-mail); Fanaroff Avroy (E-mail); Jobe Alan (E-mail); Lemons Jim (E-mail); Michael O'Shea; 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)
Cc: 'petrie@rti.org'
Subject: FW: GOT Trial Critiques and current protocol

Comments from Dr. Finer. Please let me know if you cannot open the attachments and we can resend them. Thanks See you soon Rose -----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Sunday, September 14, 2003 6:36 PM
To: Langer, John C.; Bhaskar, Brinda; Hastings, Betty J.; McClure, Beth; Gard, Charlotte; Kandefer, Sarah; Das, Abhik; npeters@wfubmc.edu; auten002@mc.duke.edu; nxs5@po.cwru.edu; lucmille@iupui.edu; ae5357@wayne.edu; Georgia.E.McDavid@uth.tmc.edu; ellen_hale@oz.ped.emory.edu; grisbyca@email.uc.edu; mbball@leland.stanford.edu; ahensman@wihri.org; cotte010@mc.duke.edu; mcw3@po.cwru.edu; martin.l.blakely@uth.tmc.edu; vanmeurs@leland.stanford.edu; BENJA005@onyx.dcri.duke.edu; bvohr@wihri.org;

Brenda.H.Morris@uth.tmc.edu; WOh@wihri.org; sshankar@med.wayne.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; barbara_stoll@oz.ped.emory.edu; aaf2@po.cwru.edu; Jobea0@chmcc.org; abbot.laptook@utsouthwestern.edu; Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD); Petrie, Carolyn
Cc: Neil Finer; Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD)
Subject: Re: GOT Trial Critiques and current protoco

Hello Everyone
I know that we have a 2 hour meeting on Wednesday to discuss the COT Protocol. We have received significant suggestions etc and in order top facilitate a discussion I have prepared a response to all the questions asked.
It is attached and I would ask that you bring it with you, as well as the revised protocol, also attached. I thank everyone for their responses, and look forward to a good discussion in DC. Carolyn, could you bring about 5 -6 extra copies of each to the meeting or more as you see fit for those who may not have been able to bring a copy. Travel 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

August 21, 2003

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 compare with animals who were ventilated from birth.[11]

1.4 Human Experience: Ventilatory Support

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[12]. 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[13]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[14] 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.

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.[15] 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[16]. 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[17]. 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[18]. 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.[19] 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)[20]. 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[21] 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[22], 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.[23] 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.[24] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[25]

There are currently no studies which have prospectively compared early 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.[26] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[27] 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 reqarding 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. [28]

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.[29] 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.[303132] 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.[33] 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.[34]

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.[35 36] 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.[37] 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))[38]. 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).[39] 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%).[40] 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.[41] 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.[42] A subsequent trial conducted in Australia that compared SpO2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months, but resulted in increased duration of oxygen supplementation.[43]

More recently 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.[44] 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.

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.[45] 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[46] 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 (≤ 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	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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 to 27 completed weeks (up to 27 6/7th) 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. 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 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) 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 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

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.

TREATMENT Group

Overview:

Treated infants will receive CPAP from birth, and if intubated for resuscitation, they will receive surfactant as soon as they are stable. If a Treatment infant requires more than 50% Oxygen for more than 60 minutes following delivery, they will be intubated at that time and

receive surfactant.

Protocol:

Early CPAP – Treatment Group - Both Strata - 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 7– 8 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.

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 receive 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 60 ± 15 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant.[27,474849] 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.

Once intubated, Treatment infants should receive surfactant as soon as they are stable.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20 or nasal SIMV.

All non-intubated Treatment infants will be evaluated at 60 ± 15 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 ≥ 90%, for a minimum of 15 minutes at any point within this period will be immediately intubated and given surfactant. For infants with rapidly changing inspired oxygen requirements, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SpO2 ≥ 90%

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 24 ± 2 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants: *These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCO2s and require higher FiO2 before intervention*

Infants ***may*** be intubated in the NICU, and surfactant given ***(first 96 hours)***, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 ≥ 90% (using the altered Pulse

Oximeters)

- A pH < 7.20 – 7.25 and/or an arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, for example a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 24 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20 - 7.25, (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 – 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

These criteria will continue in effect for 28 days from birth.

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.

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

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 provides a significant survival benefit. This approach will be used for the 24-25 wk strata. The 26-27 week infants will receive early surfactant (60 minutes ± 15 minutes if they have evidence of respiratory distress and an oxygen requirement > 40%. Control infants of 26- 27 weeks may receive prophylactic surfactant (within 15 minutes of birth) at the discretion of the Neonatologist.

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 in the delivery room.

Control Infant Protocol

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant by 60 minutes ± 15 minutes if they meet the following criteria

- An FiO_2 >0.4 to maintain an indicated SpO2 ≥ 90% using study oximeter
- The use of CPAP and an FiO2 > .30 (Once the FiO2 is > .30 the infant must be intubated.)
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 ± 9.9 torr and the pH was 7.3 ± 0.1) (arterial or capillary samples, if venous subtract 5 torr from PCO2)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 ~~the~~ centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Current Protocol ~~for~~ ensures an evidence based intervention with prophylactic or early surfactant for all enrolled infants apart from those who are stable and remain on less than 40% Oxygen, and requires ~~-~~intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25(arterial or capillary samples, if venous subtract 5 torr from PCO2)
- 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 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

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 intubation criteria, apart from the need for CPAP, for more than 4 hours, intubation should be performed.

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.

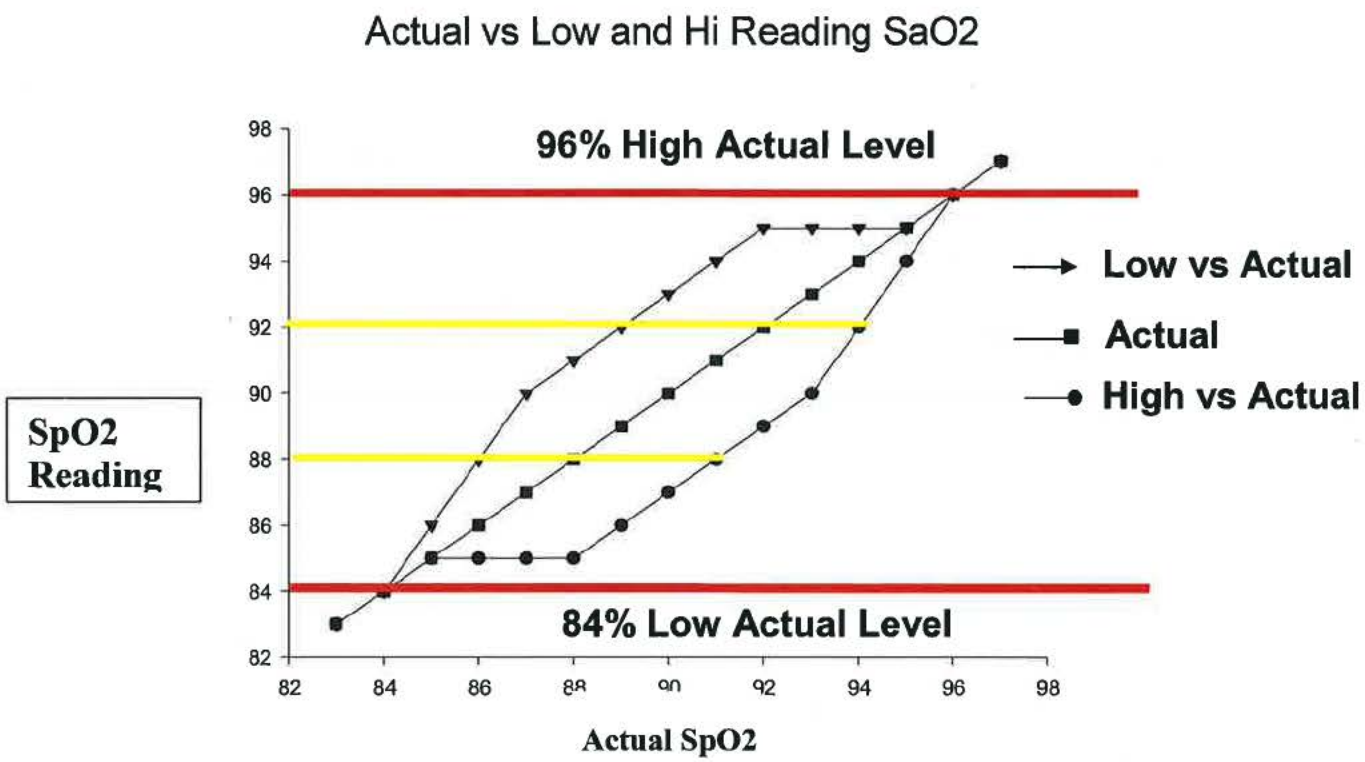
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.[505152]. 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 (should?) be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[53]

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)[54]
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 ≥ 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 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.

13 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

14 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

15 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

16 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.

17 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.

18 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.

19 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.

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

21 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.

22 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

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

24 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.

25 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.

26 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.

27 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

28 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

29 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;

30 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

31 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

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

33 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

34 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

35 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

36 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

37 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

38 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

39 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

40 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.

41 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

42 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

43 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

44 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

45 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

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

47 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

48 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

49 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

50 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

51 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 .

52 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

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

54 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

Response to Critiques of COT Protocol: Sept 14, 2003

Q.The feasibility of the study was a great concern for a number of reasons including the complexity of study design, the difficulties of obtaining consent for such a complex trial from women in extremely preterm labor, and the problems of identifying and enrolling study candidates at all hours (even though we have in house fellows or faculty every night).
This is of greatest concern with infants at 24 weeks gestation and the need to in essence know if an infant will be given "full resuscitation" prior to delivery (in order to randomize and have every thing prepared prior to delivery). For right or wrong, we do triage many infants at 24 weeks gestation and the determination to resuscitate is determined by the provider at the time of birth. In addition, it is very difficult to envision discussions with mothers about the issue of viability/use of resuscitation at this gestation, and simultaneously explaining a study of the scope and magnitude of COT. We cannot reconcile obtaining consent before delivery for a fetus that in our hospital may not be given care. The question of intention to treat, and what happens to an infant who has been consented, randomized, and then at delivery is not supported has not been answered. A related consent issue is the mother who comes to L & D and rapidly progresses to delivery before she can be consented. It is difficult to estimate the number of women who fulfill such criteria, but use of a waiver may help for this sub-group of study candidates.

A.We believe that this study is complex but doable by the Network. We have experience with pre-delivery consent and found that it worked well for the DR CPAP such that waiver was infrequently required (13/104). This population is usually consulted by Neonatology prior to delivery and we would use this opportunity to discuss the protocol and obtain consent.
The DR CPAP used a randomization by site by week which facilitated the randomization, but led to an imbalance. This would also require a separate randomization for the pulse oximeter, but that could be done by a phone call or envelope or pre-labeled POs. We can certainly discuss whether there is support for such a methodology, which would not separately randomize by strata, if it were to be kept simple. In addition this methodology does not allow for concealed randomization, but the use of envelopes or any other method still allows some time before the intervention where the team is aware of the selected approach. Using a site by week or day etc methodology also randomizes infants of multiple pregnancies to the same arm, which may be appealing to parents. In addition it is much less stressful for the resuscitation teams who would essentially approach all infants on their watch the same way. If we used a daily schedule, we would suggest that shift change in the morning would be the logical time to institute the next allocation.
We would anticipate using double sealed envelopes that would indicate the randomization to either Control/Prophylactic Surf or Treatment/CPAP and a second code indicating the number of the Pulse Oximeter to be applied within an hour of birth. The center would be supplied with a number of POs with unique identifying numbers. The teams would be asked to have surfactant available for all such deliveries, as Treatment infants who require intubation for resuscitation will also receive surfactant in the DR. We

have discussed a Waiver but believe that most IRBs may be reluctant in view of the lack of evidence indicating that CPAP and prophylactic surfactant are both evidence based and being used equitably by the sites. This issue however, can be further discussed, and as for DR CPAP, some sites may want to request a waiver. We would encourage such an application.

The delivery room interventions are very straightforward – All Control infants apart from those who appear stable < 30% in the 26-27 week strata are intubated for surfactant and taken to the NICU for continued ventilation and weaning. All Treatment infants receive CPAP/PEEP and may only receive surfactant in the DR if intubated for resuscitation. From DR CPAP we would anticipate that about 50% of the 24-25 week strata will be intubated in the DR and they will receive surfactant at that time. We are then providing an early window to give surfactant to the Treatment infants to provide them with the added benefit of this intervention. It should be noted that for DR CPAP which also enrolled at all hours, hat the coordinators were usually not in the DR.

The question is raised regarding an infant who is consented and randomized and then does not receive full treatment. We would suggest that they be analyzed as intention to treat, and would hope that these occurrences are few, and balanced between the arms. We have added a 15% attrition, which may deal with a small number of such situations. This did occur in DR CPAP, where care was withdrawn after resuscitation for a number of reasons. These infants were all included. If no resuscitation is provided, we will provide for an indication of this on the delivery room form, and discuss with Ken and RTI how to deal with these situations. This would be the category of consented, randomized and not treated, or consented, and not randomized depending on the circumstances.

Q"*control infants should all be intubated in the DR and receive surfactant within 15 minutes; forced extubation to NCPAP or NSIMV should not be permitted. We felt that such a design would permit the needed evaluation of DR-CPAP with prophylactic surfactant*"

A. We agree and this is the design with the exception that those not requiring > 30% Oxygen or CPAP by10-15 minutes could avoid intubation. For a cleaner design, intubation of all control infants would be better and evidence based, and avoid the need to consider subsequent intubation criteria for this group. This must be balanced by the knowledge that once intubated, these infants should then meet extubation criteria, which could result in longer intubation than is currently practiced in a given institution. This should be balanced by the fact that less Treatment infants would be intubated than are done as per current practice.

Q. With respect to the design, multiple faculty members had major reservations about foregoing prophylactic surfactant, particularly when the trial's current design would not allow a determination of whether CPAP/PEEP administered in the absence of prophylactic surfactant produces outcomes worse than CPAP/PEEP administered with prophylactic surfactant.

A. Our study is designed to answer the question of whether the use of early CPAP/PEEP followed by CPAP and a permissive approach will produce respiratory outcomes

equivalent or better than prophylactic surfactant with a more conventional strategy. The VON trial will have 3 arms, one of which will be early Surf with extubation etc. We believe that the question that we have asked is as important as the question being posed, and we cannot ask every question in this trial. In addition, the Network does not currently uniformly provide prophylactic surfactant, and thus this trial may benefit any enrolled infant. The practitioners of early CPAP believe that the use of early CPAP is as effective as surfactant, and this is borne out by the decreased use of surfactant at Columbia compared with Boston centers (Van Marter 2000), and a lower BPD rate. In addition there is animal data which indicates that early CPAP, especially at 8 cm H2O produces improvement in oxygenation equivalent to surfactant administration (Probyn et al, PAS 2002)

Q."Given the evidence of the benefit of prophylactic surfactant, the complexity of the current design, the likely length of the study, and the high likelihood of protocol violations I would not favor the trial as currently designed.

A.This is an interesting comment because this and many other centers do not practice the use of prophylactic surfactant in the population being studied here, and this especially true for the infants of 26-27 weeks.

Q.The use of delivery room surfactant for the control group strata of 24-25 weeks represents a major practice change. There is concern regarding a long learning curve, working through the logistics of getting the surfactant to the delivery room, and the drain of resources on the NICU by the longer period of time and the additional personnel needed in the delivery room. Furthermore, in a delivery service that has on average 40 deliveries per day (and has had up to 87 in one day!!!), the issues of communication between Obstetrics and the NICU is not to be underestimated. The latter represents areas where we have limited control, and thus may limit our success of a major change in practice in the delivery room. We have been attempting (with good success) to provide early rescue surfactant and administer surfactant in the first hour of life. If we were to combine a NICU/prophylaxis approach without using a CXR, we are pretty confident that surfactant could be given within 30-40 min following birth

A.This nicely presents the balance within the Network of the use or lack thereof of DR prophylactic surfactant. Wow!! This place could do the study by themselves!! We had many discussions about the relative benefits of prophylactic and early surfactant, and they have never been really tested against each other. Both are good, and most assume that prophylaxis is better, but many studies were pre antenatal steroids, and some were pseudo-randomized, so we probably do not have the final answer. In addition, prophylaxis overtreats with 40-60% of the infants who may not have reached rescue criteria, depending on the criteria. Early is usually less than 2 hours, selective was somewhere between 6 and 24 hours, and the references to the Cochrane data is shown.(Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software, Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software)

Q..*In assessing oxygen saturation goals, it was agreed that this is question of central importance but that the study would be meaningful only if there was great effort to regulate FiO2 and adhere to saturation goals.*

A.We partially agree, and believe that even if a great effort is not made, the groups will have significantly different SpO2 ranges, which may lead to significant outcome differences. It is possible that our different ranges are too close to each other, but we have chosen them to stay within the 85% to 95% that most are currently comfortable with. If our study shows a non-significant trend, a subsequent trial can evaluate different and perhaps more separate ones.

Q.The highest rated design option was to eliminate the delivery room component (allowing faculty to routinely use both CPAP and prophylactic surfactant and to enroll infants after NICU admission) and use a factorial design to simultaneously assess

conventional vs. permissive (conservative) ventilation (with different criteria for intubation and extubation)

conventional vs. conservative saturation goals.

A.This design suggests that CPAP plus surfactant in the DR is the best approach, but this approach has never been tested by anyone. There is a belief that these may be equivalent interventions, as noted above. In addition, we would be selecting an approach used by almost no one in the Network, to our knowledge. Centers that use early CPAP tend to delay intubation for surfactant, and centers that intubate in the DR, may not be using CPAP, and if they did, would only be using it for the time prior to intubation.

Q.Conduct a 3 armed ventilation trial (adding group given DR CPAP + prophylactic surfactant) and eliminate the evaluation of different oxygenation saturation goals. This was the 1st choice of one faculty member and the 2nd choice of 3 faculty members, though they were aware such a trial was in process outside the Network (but would probably not resolve the issue).

A.VON is pursuing such a methodology, and we wish them luck. Our trial is complex enough, novel, and will address different issues so as to be complimentary to the VON efforts.

Q.The need to define surfactant re-dosing criteria.
Is there any restriction on what kind of surfactant can be used

A.The following has been added to indicate "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.

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers recommendations for redosing intervals.

Q.The need to initiate caffeine therapy early in the infants in the treatment arm

A.Agreed and we have added the following

"**Use of Caffeine:**

Caffeine may (should?) be administered 2 hours prior to planned extubation, and for any clinically significant apnea.

Q.The need to obtain consent prior to delivery for study patients and to randomize only those infants whose mothers had received at least one dose of antenatal steroids prior to delivery.

A.This has not been addressed and we are unclear whether this should be done. All infants are at risk for CLD and ROP< these infants even more so. Why should they be denied entry? Randomization should create an equal number of such infants, and no study to date regarding surfactant or post natal steroids and no Network study to our knowledge has use such a methodology.

Q.The factorial design of the trial was concerning because of two separate primary outcomes. The rationale for linking the two studies was unclear. Also the potential for having interactive effects which could not be quantified was concerning, particularly if those effects might mask a potential benefit of one of the interventions. If there is scientific rationale to look at the effect of DR CPAP/permissive ventilation and SpO2 ranges on death/BPD, that would make the case for the factorial design much stronger in our view.
There is a high chance that the study could be stopped early for one reason, to the detriment of the factorial designed second question.

A.We have discussed this issue with Ken and we believe that while this is a factorial by design, we are essentially prospectively enrolling infants into 2 simultaneous randomized trials, the interventions of which they would receive anyway in a non-random fashion. Note that the Network does not practice prophylactic surfactant, and there is little agreement about acceptable SpO2 ranges between centers. We will be able to evaluate additive effects, and if an interaction is powerful enough, we will clearly recognize it. Since we currently combine in some way these clinical approaches, addressing them through a clinical trial will result in balanced patient allocations to each of the 4 cells. The Network is somewhat concerned regarding the SAVE trial, but there is currently little if any evidence to suggest that any arm of this trial would be harmful. Indeed. There is potential benefit to each arm if one believes the current evidence in that prophylactic surfactant is an evidence based intervention, and higher SpO2 may decrease or increase severity of ROP (STOP-ROP, Tin et al), while lower SpO2 may decrease BPD (BOOST, STOP-ROP), and there is substantial interest and preliminary data supporting early CPAP.

Q.Many faculty felt that one of the most important questions is still the role of bubble CPAP

A.We agree and would like to use the Bubbleflow. We are discussing with Fisher&Paykel this possibility, and we may have to file an IND. They are trying to satisfy the FDA at present, and it is conceivable that this trial could produce some evidence toward that end. There is recent data that suggests that bubble CPAP offers no advantages to gas exhange (Morley et al PAS, 2003)

Q.Some faculty questioned the need for different intubation and extubation criteria the criteria for intubation (CO2 65 and extubation CO2 60) are hard to reconcile

A.We are trying to maintain a significant difference between the ventilation management protocol and use stricter criteria for the Treatment infants. There were inconsistencies in the PaCO2 and SpO2 criteria that we have removed, and now the intubation and extubation criteria are similar within a group. We have specified actual criteria to ensure such differences. One issue not previously addressed was unplanned extubation in the Control infants and we have now added the following

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 intubation criteria, apart from the need for CPAP, for more than 4 hours, intubation should be performed.

Q.Some faculty raised the issue that intubation/extubation criteria would change with the masked high and low sats and were concerned that this could affect the duration of ventilation or the timing of intubation.

A.We believe that the use of the Study SpO2 ranges would effect decisions by only a 3-4% noted SpO2 difference and that there is currently a wide range of acceptable SpO2 and PaO2 that are utilized throughout the Network. We do not believe that the use of the study Pos with altered ranges will effect clinical decisions to a mjor degree, and the knowledge that values below 85% and above 95% are real will ensure that for these deviations all staff will know the real SpO2 value.

Q.It was strongly suggested that the COT committee consider dropping the oxygenation part of the study and concentrate on the CPAP component of the trial. Keep in mind that the Network feasibility study was for the CPAP trial alone. Also the experience from STOPROP trial should be reviewed to see whether the oxygenation component of the protocol is doable or not

A.As previously explained we currently vary the acceptable SpO2 between centers, and there is preliminary data that lower SpO2 may be better (Tin et al, Chow et al). Both STOP ROP ands BOOST studied infants > 32 weeks PCA or at pre-threshold (about 34 weeks PCA) and no study has prospectively evaluated early ranges of PaO2. With the blinding, we believe that this portion of the study is much easier than the ventilation intervention.

Q.How do we handle multiple gestations? Exclude, enroll all fetuses, enroll only one, if so which one

A.Frequently asked. In response we ask whether any Network study has enrolled multiples as a unit. We had asked about this during the design of the DR CPAP. We are comfortable with either method, and parents would probably prefer unit randomization, but that may introduce imbalance. This study should follow the general approach being taken for all current trials such as phototherapy which randomizes all multiples separately.

Q.How about dropping 24 and 25 weekers and expand gestation strata to 28 weeks. In other word, change inclusion criteria to 26/0 to 28 completed weeks.

A.The group at greatest risk and least well studied is the younger strata. We may be the only group willing to evaluate this group.

Q.Concerns were expressed regarding the permissive ventilation strategy. Is pH >7.20 for extubation realistic. It maybe better to give a range of perhaps, 7.20 – 7.25 to allow for some flexibility.

A.Done, and to demonstrate the differences in the Network between sites I have added a response from Cincinnatti
For study purposes, it is OK to wait for severe apnea or pH < 7.2 and pCO2 > 60 and fiO2 > 0.5 to intubate infants 24-28 weeks. 10 Yes 0 No 1 ?

Q.Same applies to the rate of ventilator for extubation in the treatment group. Rather than < 15, use a range of 15-20

A.Done
Q.*A couple of faculty members expressed serious concern about high O2 range of up to 95%. They would be willing to go along with 92 0r 93 % . It was pointed out that a paper in this week New England Journal showed better outcome in regards to oxygenation target at 91-94 % as compared to 95-98%. Should we consider dropping the range to 90-93, not 90-95% ?*

A. As discussed by Dale, the BOOST trial started at 32 weeks PCA, and the ranges chosen are somewhat arbitrary. There are no previous data to use for any chosen range and so we have tried to choose different ranges within the 85% to 95% range, based on previous data. We believe that most sites will want larger rather than narrower ranges for alarms and thus we are aiming to have significant differences within the 85% to 95% range.

Q.It was also suggested that the COT Committee performs a survey for current practice in regards to the intubation and extubation criteria and practices among centers with the goal of setting up criteria that are as close to current practice as possible.

A.We will loosely poll at the Steering Committee meeting. If further information is deemed helpful, it can be obtained. We are probably recommending criteria that do not exactly match any center's current practice, and that applies particularly to the Subcommittee members. These criteria are thought to represent a reasonable consensus, and maintain separation between the groups.

Q.The most consistent concern was a lack of standardization of modalities of therapy, and with acknowledgement of different delivery systems having different levels of effectiveness, the Network should strongly consider standardization of the CPAP device.

A.We will attempt to obtain the Bubbleflow for this trial as noted above. Attempting to use another apparatus for standardization would be expensive, and without any evidence basis.

Q.The group also voiced concern over the perceived 3 different aspects of management to be investigated in one trial; early CPAP vs intubation early, permissive vs more aggressive ventilation, and the factorial design for O2.

A.This is a complex trial, and the CPAP and permissive approach are part of a single strategy, much modified to be acceptable within the ranges of current Network strategies. This will be compared to prophylactic surfactant and a more conventional ventilatory approach. The longer we delay, the greater will be the drift toward a more permissive approach by all centers without adequate evidence.

Q.With ongoing study in Benchmarking, there may be significant management practices that he committee may want to standardize for the study. We believe that failure to standardize "Benchmarking" findings or best care will obscure the results as mechanical ventilation and early NCPAP are only part of the multifactorial etiology of BPD.

A.By the initiation of this trial, benchmarking will be close to completion. We have tried to suggest a minimal of standardized approaches, and indeed are testing the comparability of prophylactic surfactant to early CPAP. The Network has been aware that prophylactic surfactant is an evidence based intervention, but this approach is not standardized within the Network. This study will force such an approach for the Control infants, and the results will aid in determining future best practice. There is no currently accepted standard care regarding SpO2 limits.

Q.Nasal CPAP delivered by high flow nasal cannulae is not considered but has become standard practice in many nurseries.

A.Nasal Cannula may deliver CPAP but it is unregulated and unmeasured, and we are not prohibiting its use for infants subsequent to the discontinuation of CPAP. We would not, however encourage its use till better studied.

Q.Concern was raised about the intubation criterion of an FiO2 0.50 to maintain an SpO2 ≥ 88%. We would not know this because the limits on the pulse ox for the low range is 85-89%.

A.We have standardized this criterion to a SpO2 > 90%, the midrange of the SpO2 target range for both groups, and thus the Actual SpO2 could be 87% or 93% approximately. There is some information that currently SpO2 values may be somewhat optimistic, and all caretakers will be aware if the actual SpO2 if the true SpO2 is < 85% or > 95%. This study is designed to determine if such lower limits are beneficial as suggested by Tin et al and Chow et al.

Q.Page 12 – The injunction that "extubation must be attempted within 12 ± 2 hours . . . would be difficult if your clinical judgment dictates otherwise. For instance, extubation criteria are met but the child has a ductus, is developing pulmonary edema and therefore at risk for pulmonary hemorrhage.

A.We have changed this to a 24 hour period to allow more flexibility, and not force extubation, and re-intubation may delayed for up to 48 hrs

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 24 hours if all of the following criteria are met:***

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. ***The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.***

Q.Permissive ventilation adds another confounder into the study and may cloud the outcome. It is another approach that needs to be validated. This may be further exacerbated by statements like "the minimum" criteria proposed on page 13 (i.e., intubation may be delayed according to clinical preference).

A.The Network would agree that permissive hypercapnia needs further testing. The SAVE trial was an attempt and the COT trial would provide adequate power to answer this question. The treatment group is intended to allow less intubation and less exposure to ventilation and determine if this approach is effective in reducing BPD.

Q.Protocol violations will be extremely common. Particularly night crews changing ventilation
Concern was raised about the time and monitoring of such a complex study to assure that compliance is high. The results of the feasibility trial (re: compliance) were not convincing given the limited time and intervention relative to the COT trial. There will need to be a hard look at what is needed in terms of Network Coordinator/PI time to realistically facilitate this study. The level of interaction that may be necessary between study personnel and attending staff is such that there may be negative spill-over to other Network endeavors (the latte is my personal concern).

A.We believe that the current iteration is somewhat simpler, and that additional surveillance may be required as suggested from Alabama
"There is concern about the need to monitor compliance and the agreement is that there will be a need to have a research coordinator assess protocol compliance twice daily with twice daily feedback (at least initially) to the caretakers (and PI/designated opinion leader as needed). This should be budgeted into the capitation".

Q.Allowing use of the Neopuff in the control group will reduce the potential differenced between the groups, making the testing of CPAP/EEP in the DR invalid

A. We hope that most of the control infants will be intubated in the DR for surfactant and the continuing use of CPAP in such infants will constitute a criteria for intubation. Therefore the use of the Neopuff would not confuse this trial. The Treatment infants will not be intubated in the DR except for resuscitation intervention. In addition, this trial is to evaluate a total approach involving early CPAP and a continuing permissive approach, not just the use of CPAP/PEEP in the DR. Even the DR CPAP feasibility trial was not powered to evaluate the benefit of DR CPAP.

Q.What will you do about kids who need to have upper and lower saturations looking for shunting?

A.Do what you normally do which is to drive the SpO2 > 96-98% and look for pre vs Postductal shunting. We will ensure that for such purposes and second identically altered PO will be available for such an evaluation. Any pre- vs post ductal difference will be noted, and all values > 95% are actual.

Q.Can you randomize an infant into the oxygen study if he is missed consent for the DR management portion of the trial? (or if the parents refuse that part?)

A.Not with the current design.

Q.You need some criteria to allow for intubation for some degree of excessive work of breathing

A.What is the data to support this request? We believe that we need to use objective criteria as are listed. Clinicians will make the ultimate decision, and we may have to analyze how often this happens.

Q.What if you don't have arterial gases? how do you use PaCO2 values? pH ? use VBG or CBG?

A.In the absence of an arterial line, a capillary sample is preferred, but venous values may be used, and should be interpreted as reading 5 torr higher than the arterial PaCO2. This has been added to the protocol

From:	Wally Carlo, M.D.
To:	"Edward Donovan "; Higgins, Rosemary (NIH/NICHD); "nfiner@ucsd.edu "
Cc:	"William_Oh@brown.edu "; "ALAN JOBE "; "Barbara Warner "; "James Greenberg "; "Jean Steichen "; "Jeffrey Whitsett "; "Jon Fridriksson "; "Self "; "jlemons@iupui.edu "; "goldb008@mc.duke.edu "; "sshankar@med.wayne.edu "; "alapto@mednet.swmed.edu "; "sduara@miami.edu "; "aaf2@po.cwru.edu "; "petrie@rti.org "; "poo@rti.org "; "dstevenson@stanford.edu "; "dale_phelps@urmc.rochester.edu "; "Jon.E.Tyson@uth.tmc.edu "; "moshea@wfubmc.edu "; "Richard.Ehrenkranz@yale.edu "
Subject:	RE: COT
Date:	Tuesday, September 09, 2003 9:08:38 PM

I also want to share our group feedback. I sent the info to Neil last week, but as everyone is sharing it, here it is.

Our group was 100% supportinve of the factorial design and the study in general. There is concern about the need to monitor compliance and the agreement is that there will be a need to have a reserach coordinator assess protocol compliance twice daily with twice daily feedback (at least initially) to the caretakers (and PI/designated opinion leader as needed). This should be budgeted into the capitation.

On the surfactant issue, we will have to change our pracitce, but agree it is a reasonable apporach.

Wally

-----Original Message-----
From: Edward Donovan
To: higginsr@mail.nih.gov; nfiner@ucsd.edu
Cc: William_Oh@brown.edu; ALAN JOBE; Barbara Warner; James Greenberg; Jean Steichen; Jeffrey Whitsett; Jon Fridriksson; Self; jlemons@iupui.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; alapto@mednet.swmed.edu; sduara@miami.edu; Wally Carlo, M.D.; aaf2@po.cwru.edu; petrie@rti.org; poo@rti.org; dstevenson@stanford.edu; dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; moshea@wfubmc.edu; Richard.Ehrenkranz@yale.edu
Sent: 09/09/2003 1:24 PM
Subject: COT

I sent the protocol to Cincinnati neonatologists, but only received feedback from 2.
So I sent the following email questionnaire and received 11 responses summarized after each question.

"This study enrolls infants 24-28 weeks GA prior to delivery with parental consent. It is a factorial design, meaning infants are simultaneously randomized to 2 different interventions: maintenance of optimal lung volume (not too big and not too small) and low vs high oxygen saturation. The outcomes are death or BPD and threshold ROP. Here are the questions. Your answers will be only shared anonymously.

1. It is very important to evaluate the impact of maintenance of appropriate lung volumes on risk of BPD. 11 Yes 0 No

2. It is very important to evaluate the impact of different levels of oxygen saturation on outcomes of infants 24-28 weeks GA. 11 Yes 0 No

3. Keeping the oxygen saturation between 88% and 92% with alarm limits 85-95% will cause inappropriate difficulty with the care of the infant OR with the well-being of the bedside nurses. 0 Yes 11 No

4. It is appropriate, for study purposes, to give surfactant before age 60 minutes to all 24-28 week infants who require more than 50% O2. 10

Yes 1 No

5. For study purposes in intubated infants 24-28 wks, it is appropriate to wait until pCO2 is < 50 and fiO2 < 0.4 and MAwP < 8 to extubate. 6 Yes 5 No [the "No's" emphasized that 50 was "too low".

6. For study purposes, it is OK to modify the pulse oximeters so that the O2 saturation reads either 3% low or 3% high. 10 Yes 1 No

7. For study purposes, it is OK to wait for severe apnea or pH < 7.2 and pCO2 > 60 and fiO2 > 0.5 to intubate infants 24-28 weeks. 10 Yes 0 No 1 ?

Hope this is helpful.
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 <http://www.cprc-chmc.uc.edu>

From:	Wally Carlo, M.D.
To:	"Neil Finer"; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara
Subject:	FW: COT trial
Date:	Friday, August 22, 2003 6:16:10 PM
Attachments:	COT ltr to PIs 22Aug03.doc COT study Aug 19 03.doc

---

The letter may give the wrong impresssion that this is a study of DR/CPAP vs early surf but the experimental interventions are more encompassing including lung injury protective strategies (hypercapnia, hypoxemia) in a factorial design. It will be obvious in the protocol, but the letter may confuse the PIs. Wally

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Friday, August 22, 2003 2:00 PM
To: M. D. Abbot Laptook (abbot.laptook@utsouthwestern.edu); 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. 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); Wally Carlo, M.D.; Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org)
Cc: aRose Higgins (higginsr@mail.nih.gov); Poole, W. Kenneth; M. D. Alan Jobe (Jobea0@chmcc.org); Alice Reardon (Houston) (Alice.J.Reardon@uth.tmc.edu); Brian Johnston (Brown) (BJohnston@wihri.org); Carolyn Grier (CWRU) (axt25@po.cwru.edu); Debbi MacDougall (dmacdoug@iupui.edu); Diane Timmer (Cincinnati) (diane.timmer@cchmc.org); (Estelle.Fischer@cchmc.org); Heidi Squibb (UCSD) (hsquibb@ucsd.edu); Judy Sheplow (Wayne) (Jsheplow@med.wayne.edu); (Karen.Kirby@UTSouthwestern.edu); Lisa Joo (Stanford) (lisa.joo@stanford.edu); Marsha Sumner; Mazie Tinsley (Emory) (mazie_tinsley@oz.ped.emory.edu); (renee.dunbar-scott@oz.ped.emory.edu); Hastings, Betty J.; Petrie, Carolyn; Sharon Gonzales (Duke) (gonza025@mc.duke.edu); Wendy Holcomb; Das, Abhik
Subject: COT trial

To the Neonatal Research Network Steering Committee:

Please find the following attached to this email:

- COT study (August 19, 2003) - PI: Dr. Finer
- Dr. Ehrenkranz's cover letter

Please send your department's comments to Dr. Finer by **September 15, 2003**.

Thank you,
Carolyn

DATE: August 22, 2003

TO: NICHD Neonatal Research Network PIs

FROM: Richard A. Ehrenkranz, MD,
Chair; Protocol Review Subcommittee

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

Submitted by: Neil Finer for the DR-CPAP Subcommittee

The Protocol Review Subcommittee reviewed this protocol during its conference call on August 4, 2003. Written reviews had been prepared by Jon Tyson, Seetha Shankaran, and Dale Phelps prior to the call. In addition, several members of the subcommittee, especially Jon Tyson, had a dialogue with Neil Finer during the weeks prior to and after the call. Although Neil is a member of the Subcommittee, he was requested to join the call after about 45 minutes, so that the subcommittee could attempt to achieve some consensus about the protocol.

Much of the discussion during the conference call dealt with the protocol's apparent complexity and whether there were sufficient data to support mounting a large multicenter clinical trial. Specifically, although data exist about the benefit of prophylactic/early surfactant therapy, were there sufficient data to support the treatment arm of the protocol, with the likelihood of not administering surfactant to all these extremely preterm infants. Justification of the factorial design was reviewed; during the discussion it became clear that the proposal was underpowered to look at true interactions, but adequately powered to evaluate additive effects (according to Ken this typical of most factorial studies). The primary and secondary outcomes and the proposed analytical plan were also reviewed.

Following the Protocol Review Subcommittee conference call, the COT study subcommittee had 2 conference calls to discuss and consider issues raised by the Protocol Review Subcommittee. Although some modifications were made to the protocol, the original study design was maintained, since the COT study subcommittee believed that there was a reasonable level of equipoise to perform this trial, and that a comparison of DR/CPAP and prophylactic/early surfactant was needed in an era of high antenatal steroid use.

The August 19, 2003 version of the COT study accompanies this memo. During the next several weeks, it is imperative that you discuss this study with your colleagues and that you obtain comments from them about such issues as feasibility and changes that would improve the design and make it more feasible. Remind them that this is their opportunity to have input in a study under development. Bring those comments with you to the Steering Committee meeting; if possible, send them to Neil by email by September 15th. As you will note, a COT study working session is planned on Wednesday afternoon September 17th for all PIs. The goal would be to have a relatively final protocol by the time the Steering Committee meeting concludes.

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

August 19, 2003

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]

1.4 Human Experience: Ventilatory Support

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[11]. 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[12]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[13] 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.

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.[14] 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[15]. 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[16]. 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[17]. 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.[18] 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)[19]. 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[20] 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[21], 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.[22] 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.[23] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[24]

There are currently no studies which have prospectively compared early 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.[25] Early

surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[26] 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 reqarding 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.[27]

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.[28] 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.[29,30,31] 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.[32] 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.[33]

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.[34,35] 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.[36] 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))[37]. 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).[38] 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%).[39] 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.[40] 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.[41] A subsequent trial conducted in Australia that compared SpO2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months, but resulted in increased duration of oxygen supplementation.[42]

More recently 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.[43] 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.

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.[44] 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[45] 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 (≤ 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	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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 to 27 completed weeks (up to 27 6/7th) 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. 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 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) 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 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

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.

TREATMENT Group

Overview:

Treated infants will receive CPAP from birth, an if intubated for resuscitation, they will receive surfactant as soon as they are stable. If a Treatment infant requires more than 50% Oxygen for more than 60 minutes following delivery, they will be intubated at that time and

receive surfactant.

Protocol:

Early CPAP – Treatment Group - Both Strata - 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 7– 8 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.

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 receive 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 60 ± 15 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress, and the recent results of the Vermont Oxford Network trial comparing early versus later surfactant.[27,464748] 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.

Once intubated, Treatment infants should receive surfactant as soon as they are stable.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20 or nasal SIMV.

All non-intubated Treatment infants will be evaluated at 60 ± 15 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 ≥ 90%, for a minimum of 15 minutes will be immediately intubated and given surfactant. For infants who appear unstable, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SpO2 ≥ 90%

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 ±2 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants: *These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCOs and require higher FiO2 before intervention*

Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 ≥ 88% (using the altered Pulse

Oximeters)

- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20,
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

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.

<u>CONTROL Group</u>

<u>Overview:</u>

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 provides a significant survival benefit. This approach will be used for the 24-25 wk strata. The 26-27 week infants will receive early surfactant (60 minutes ± 15 minutes if they have evidence of respiratory distress and an oxygen requirement > 40%. Control infants of 26- 27 weeks may receive prophylactic surfactant (within 15 minutes of birth) at the discretion of the Neonatologist.

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 in the delivery room.

Control Infant Protocol

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant if they meet the following criteria

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 88% using study oximeter
- The use of CPAP and an FiO2 > .30 (Once the FiO2 is > .30 the infant must be intubated.)
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 the centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Current Protocol for ensures an evidence based intervention with prophylactic or early surfactant for all enrolled infants apart from those who are stable and remain on less than 40% Oxygen, and requires intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of ***MAY*** be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

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.

.

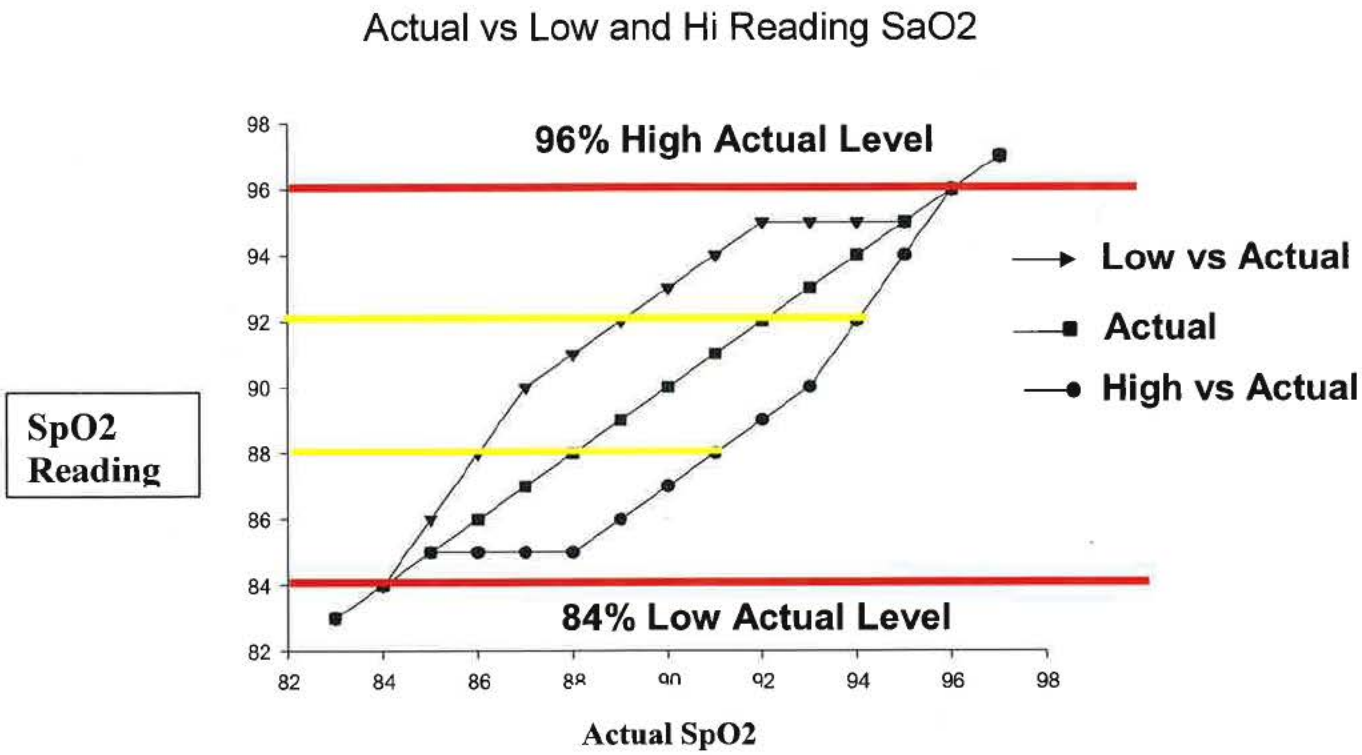
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.[495051]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants.

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)[52]
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 ≥ 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 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.

12 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

13 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

14 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

15 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.

16 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.

17 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.

18 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.

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

20 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.

21 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

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

23 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.

24 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.

25 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.

26 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

27 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

28 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;

29 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

30 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

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

32 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

33 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

34 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

35 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

36 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

37 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

38 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

39 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.

40 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

41 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

42 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

43 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

44 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

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

46 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

47 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

48 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

49 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

50 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 .

51 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

52 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 Ehrenkranz
Cc:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject:	COT Protocol
Date:	Tuesday, August 19, 2003 7:29:49 PM
Attachments:	COT study Aug 19 03.doc

Hello Richard

We have reviewed the COT trial and had 2 conference calls since the protocols committee meeting. We have decided to maintain the original design with some modifications to ensure that the protocol is understandable and that the interventions are clearly defined. We believe that there is a reasonable level of equipoise to perform this trial, and that a comparison of CPAP with prophylactic surfactant is needed. In addition, we have allowed a window for the administration of early surfactant for all enrolled infants, to ensure that if these infants have respiratory distress that they can receive this intervention once they meet criteria.

The SpO2 intervention should be an easier intervention, and allow the testing of 2 different SpO2 ranges while ensuring that caretakers are aware of true significant low (< 85%) and high (>95%) values.

The sample sizes are derived from an 80% power for the 2 primary hypothesis, with an 80% power to look at the secondary outcome of Mortality/NDI at 18-22 months. We will be able to determine additive effects of the primary interventions. The study is not powered to look at interactions between these hypotheses.

We would ask that this protocol be circulated to the Site PIs (Steering Committee) members for discussion at the sites. Either the PI or a designated study PI/advocate can then discuss with the faculty, and raise questions that can be addressed to me for discussion by our group. We would then potentially modify the protocol and discuss at the September Steering Committee meeting. Our group, including Rose, felt that it would be more informative to pole the sites for questions, rather than circulating a series of predetermined questions.

I trust that this protocol is now acceptable for circulation to the PIs.

We appreciate the detailed review provided by the Protocol Committee, and hope that the current protocol has satisfactorily addressed the concerns raised by your committee.

Regards

Neil Finer

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Cc: Poole, W. Kenneth
Subject: COT Conference call
Date: Thursday, August 14, 2003 3:17:16 PM
Attachments: COT study Aug 14 03.doc

Hello Everyone
I have attached a revised protocol with the major additions/changes in yellow. These reflect a restating of the sample size and estimates, Tables of outcomes for the various hypotheses (provided by Ken with thanks), and a preliminary change if we go to intubation for Surf for all.
I know that Shahnaz and others, me included, are concerned about intubating all for surf in the DR, but this may be the only acceptable methodology.
The original protocol still looks very acceptable to me, but I am somewhat prejudiced.
I have increased the PaCO2 to 65 torr and left the FiO2 at 50% for the treatment group for extubation.
Another thought - what if for the 26-27 week infants we use prophylaxis for surf for the controls and CPAP and a 30 minute look for surf. This group will be bigger and more likely to get away without surf, and have a higher percent that would never have had surf treatment? In most prophylactic studies about 40%-50% of infants required selective later treatment. Is this still too complicated?
Talk to you tomorrow.
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

July 3, 2003

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 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 natural surfactant, an intervention 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 precipitated by the 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 where performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges 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 demonstrated that the early use of CPAP 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]. The use of early CPAP also appears to decrease the need for subsequent surfactant use and mechanical ventilation in premature infants. 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.[6]

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 recommended 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 new technology that can be used to tightly control 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 recommended levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels will 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 [7]. The use of early PEEP improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [8,9]

1.4 Human Experience: Ventilatory Support

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 infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP soon after delivery[10]. 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[11]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[12] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that early use of CPAP was associated with 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.

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.[13] 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[14]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages.

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[15]. 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[16]. 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.[17] 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)[18]. 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[19] 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[20], 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.[21] 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.[22] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[23]

There are currently no studies which have prospectively compared early 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.[24]

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.[25] 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.[262728] 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.[29] 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.[30]

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.[31 32] 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.[33] 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))[34]. 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).[35] 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%).[36] 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 < 1000gm, there was a decrease in the incidence of ROP.[37] 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.[38] A subsequent trial conducted in Australia that compared SpO2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or neurodevelopmental outcome, but resulted in increased duration of oxygen supplementation.[39]

More recently 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.[40] 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.

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.[41] 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[42] 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 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 (≤ 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.

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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.

3). We hypothesize that the that relative to infants managed with surfactant and CMV and a high SpO2 range that the combination of early CPAP and a permissive ventilator strategy with a lower SpO2 range will individually and collectively positively impact the NDI/Mortality

outcome at 18-22 months corrected age.

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 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 threshold 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 to 27 completed weeks (up to 27 6/7th) 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. 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

Strata: There will be 2 randomization strata, infants of 24 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) and to either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent following admission, 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 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

The randomization to either a high or low SpO2 will be performed immediately following NICU admission, with a maximum allowable delay of 1 hour following NICU admission.

TREATMENT Group

Early CPAP – Treatment Group - Both Strata - 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 and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 7– 8 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.

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 receive intubation for resuscitation in the Treatment group may 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 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress..[434445] 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.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20 or nasal SIMV.

All non-intubated Treatment infants will be evaluated at 30 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 $\geq$ 90%, they will be immediately intubated and given surfactant. For infants who appear unstable, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SpO2 $\geq$ 90%

OR

All Treatment infants will be intubated in the DR following usual resuscitation practices and be given surfactant within 15 minutes of delivery, and then transferred to the NICU, receiving PPV. Infants of 26-27 weeks who are stable on room air by 10 minutes of life do not require intubation for surfactant treatment

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 ±2 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants (Only 26-27 week infant who were on RA by 10 minutes): *These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCOs and require higher FiO2 before intervention*

Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 ≥ 88% (using the altered Pulse Oximeters)
- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, for example a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 65 torr with a pH > 7.20,
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

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.

CONTROL Group

NOTE: 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 30 minutes provides a significant survival benefit

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 in the delivery room.

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the delivery room and given surfactant within 15 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in delivery room and given surfactant within 15 minutes of birth, but **MUST** be intubated and receive surfactant if requiring any supplemental Oxygen by 30 minutes.

Intubation Criteria for non-intubated Control infants > 30 minutes of age in 26-27 weeks strata: These Control infants ***MUST*** be intubated and receive surfactant if they meet ***ANY*** of the following criteria:

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 88
- The use of CPAP
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (**Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1**)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 the centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Current Protocol for ensures an evidence based intervention with prophylactic surfactant for all enrolled infants apart from those who are stable on RA at 10 minutes after birth, and requires intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of MAY be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

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 POs 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. 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%.

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 as of June 27th 2003, that this technology is workable.

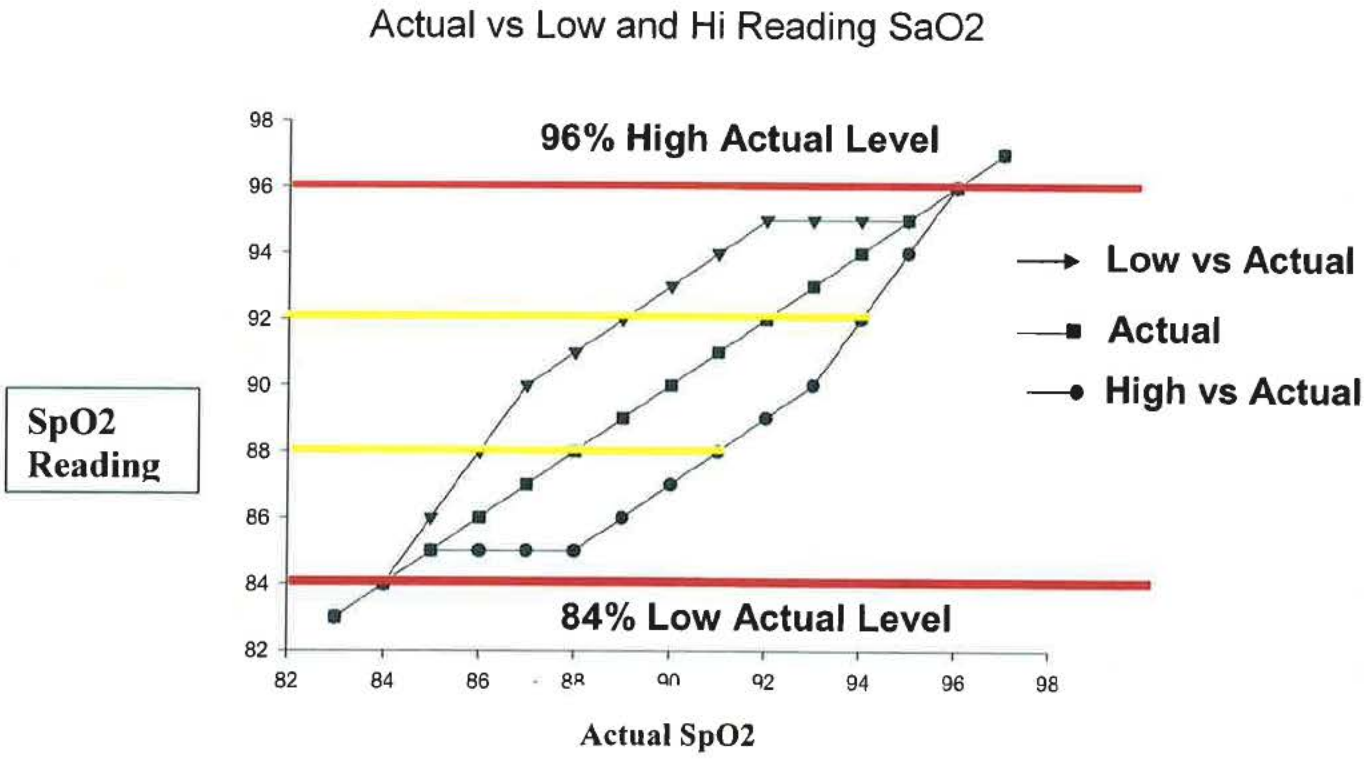
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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 96%. This will provide for an overall set of limits on actual SpO2 of 84% to 97% 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 96%. 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. 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 the PO SpO2 data was used in the DR CPAP Pilot trial

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.[464748]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants.

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)[49]
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

8.2 Sample Size

As discussed above, there are two main outcomes for the factorial design: mortality or BPD; mortality or ROP; and 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.

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 DRCPAP (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

DRCPAP	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 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

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

8 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

9 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

10 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.

11 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

12 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

13 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

14 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.

15 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.

16 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.

17 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.

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

19 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.

20 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

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

22 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.

23 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.

24 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.

25 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;

26 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

27 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

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

29 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

30 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

31 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

32 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

33 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

34 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

35 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

36 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.

37 Flynn JT; Bancalari E; Snyder ES; Goldberg RN; Feuer W, and Cassady . A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326

38 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

39 Askie,LA, Henderson-Smart,DJ, Irwig,L, Simpson, JM The Effect of Differing Oxygen Saturation Targeting Ranges on Long Term Growth and Development of Extremely Preterm, Oxygen Dependent Infants: The Boost Trial. .Pediatr Research 2002;45;348A

40 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

41 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

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

43 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

44 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

45 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

46 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

47 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 .

48 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

49 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: Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Subject: COT Trial Phone call
Date: Wednesday, August 13, 2003 8:07:49 PM

Hello Everyone
We will have a conference call Friday at 11:00 AM Eastern Time
I have suggested a brief agenda for your consideration below.
1. Do we want to proceed with the current protocol as is?
2. If not, what is our opinion about a protocol which will give all infants prophylactic surfactant in the DR?
3. This would result in the infants all being treated similarly in the DR, with the study interventions being initiated in the NICU - Aggressive weaning vs. Conventional and Hi vs. Lo SpO2
4. If we agree to this, should we increase the FiO2 and PaCO2 requirements for extubation to 60% and 65 torr?
5. In accepting this approach we will abandon the idea of testing whether DR and continuing CPAP is equivalent or better than early surfactant - are you OK with this?
6. Should we add the use of nasal (S)IMV to the support for the Treatment arm to provide further support to them after extubation? This methodology is currently used at 3 centers in some significant amount - Alabama, Yale, UCSD are the more frequent users, with some use at Rochester, Stanford, and Dallas and is evidence based.
7. We will necessarily treat more infants with prophylaxis than with later treatment - is that OK
Our aim is to get a protocol to the Network that we believe will answer important question(s), that is doable in a reasonable period of time.
The VON protocol will address the issue of early CPAP in one of their 3 groups.
I see the benefit of this modification being that we may get earlier buy-in. The Network needs to initiate more innovative trials if we are to be seen as being productive.
Do you see an alternative using early CPAP? Our previous approach was to evaluate at 30 minutes and give surf to those who fulfilled criteria at that time - there appears to be a feeling that this is overly complex - I have one additional thought - we could give surfactant to the CPAP infants and then extubate all within 30-60 minutes of admission instead of waiting till 12 hours - I think that this will create a number of unstable infants in the 24 weekers personally.
Thanks for your input
Talk to you on Friday
Neil

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT t rial
Date: Wednesday, August 13, 2003 1:19:37 PM

Rose
My previous email of this morning asked about Tomorrow or Friday and asked that you coordinate. Ed is OK for Fri at 11:00 AM Eastern.
I haven't heard from the others yet.
Neil

> ----- Original Message -----
> **From:** Higgins, Rosemary (NIH/NICHD)
> **To:** 'Neil Finer' ; Avroy A. Fanaroff, M.D. ; Edward Donovan ; Shahnaz Duara ; 'Wally Carlo, M.D.'
> **Sent:** Wednesday, August 13, 2003 9:55 AM
> **Subject:** RE: Fw: Increasing the feasibility and conclusiveness of theCOT t rial
>
> Neil
> Do you think a conference call witht he subcommittee would help to sort out some of these issues? We could do it in the next week.
>
> Let me know.
> Rose
>
> > -----Original Message-----
> > **From:** Neil Finer [mailto:nfiner@ucsd.edu]
> > **Sent:** Wednesday, August 13, 2003 10:46 AM
> > **To:** Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD)
> > **Cc:** Neil Finer
> > **Subject:** Re: Fw: Increasing the feasibility and conclusiveness of theCOT t rial
> >
> > Hi Rose and Wally
> > I absolutely agree that the surfactant data is not representative of current practice. Most of these studies were done in infants whose mothers did not receive antenatal steroids, in fact few if any of these studies provided that number. Almost all were published before 1992. In addition, as I previously discussed, there has been no good comparison between early selective surf and prophylactic use.
> > Only enrolling infants who have received surf is also a problem, because the excluded infants may benefit from early CPAP. In addition the Network does not have data on the time of surfactant administration, and we could not calculate a study sample using only infants who receive within 1-2 hours of birth.
> > The current suggestion, that we give surfactant prophylactically to all, could be amended to give the surf within 30 minutes. Infants would be randomized, all would receive surf within 30 minutes, and start on their randomized pulse oximeter on NICU admission. This would leave DR care out of the protocol. I would then assume, that the first 30 minutes of care would represent standard of care at each place.
> > One additional thought - since we are being aggressive in getting infants off ventilators and keeping them of, should nasal SIMV be available and utilized in the Treatment infants only? I know that Wally uses this approach, and so does Yale.
> > Would everyone be available for a short conference call tomorrow or Friday say at 11:00 Easter time?
> > Could you reply to all of us. If this is possible, perhaps Rose could organize?
> > Many thanks
> > Neil----- Original Message -----
> >
> > > **From:** Higgins, Rosemary (NIH/NICHD)
> > > **To:** 'Wally Carlo, M.D.' ; 'Neil Finer' ; Shahnaz Duara ; Edward Donovan ; Avroy A. Fanaroff,

M.D.
Sent: Wednesday, August 13, 2003 5:39 AM
Subject: RE: Fw: Increasing the feasibility and conclusiveness of theCOT t rial

Hi
One point to consider - surfactant is one of the best studied therapies for preterm babies. However, the vast majority of these studies showing improvement in survival were done in the era of low use of antenatal corticosteroid therapy to accelerate lung maturation(i,e, some almost 20 years ago, - Shapiro et.al.). In addition, practice changes such as double walled incubators with high humidity and less aggressive fluid management have come into play. I think that mandatory surfactant for all of the 26-27 week infants needs careful consideration.

Rose

-----Original Message-----
From: Wally Carlo, M.D. [mailto:WCarlo@PEDS.UAB.EDU]
Sent: Tuesday, August 12, 2003 7:41 PM
To: 'Neil Finer'; Higgins, Rosemary (NIH/NICHD); Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Subject: RE: Fw: Increasing the feasibility and conclusiveness of theCOT t rial

I think instead of mandating surf for all, a simpler solution is to include infants only if they have received surfactant. The suggested practice would be to use prophylactic surfactant as the literature suggests but if on selected infants the clinicians prefer not to do it, that would be ok, the infant would not be in the trial. we could have a time limit for entry (eg 2 hours or so). If surf and consent are not done by this time, they are not randomized. I would prefer this revised version with not mandating the DR care. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Tuesday, August 12, 2003 6:22 PM
To: higginsr@mail.nih.gov; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial

Thanks Ed
You are correct - Option #3 from Jon would see all infants get prophylactic surf. I can live with that as I also don't believe that DR CPAP alone is the answer. We need to obtain and maintain FRC - CPAP will help maintain and initial PPV will help obtain FRC. Surfactant will obviate establishing FRC, and if all infants get early surf - we can argue about how early, we can then test the ventilation strategy and see if reducing the duration is crucial to reducing the BPD rate and severity.
It sounds like I should modify the protocol to include early/prophylactic surfactant for all - that would make the initial approach very easy even if it involves a significant change in practice at some centers. Ed, your center is probably the most aggressive at using early CPAP. Would your group be averse to early surfactant and then aggressively attempting to extubate the Treatment arm?
Would everyone be willing to accept this change, or do you want to try to push the current version ahead.
I am of 2 minds (probably more) - 1) Lets get this study done ASAP with the factorial in a manner acceptable to the majority of sites
2)Lets stick to our guns and see if we can convince the rest of the Network to agree. I suspect that the latter will eat away at our time and enthusiasm. In addition, giving all surf in the DR is consistent with good evidence, and while it

will not address the issue of whether early CPAP is as good as early surf, it will allow adequate evaluation of an aggressive weaning strategy and the use of continuing CPAP in the NICU. In our current experience, we are giving DR surf to all less than 27 weeks - we started this after the DR CPAP finished awaiting the next intervention. We do however attempt to the stabilize the infant and the surf is sometimes delayed till 15 minutes or later. However, we are extubating as soon as is possible, and usually by the following morning whenever feasible. The question that would remain - are the 2 arms of the Vent protocol sufficiently distinct?

If we want to move in this direction, what would you all accept as the latest time to give the surfactant - 15 minutes, 30 minutes? I would suggest that we give in the DR < 20 minutes, but could live with the traditional 15 minutes.

You know, the SpO2 will be the easier part of this trial. We need to think about alarm limits and how important they are. Are we going to rigidly specify or merely provide the range ie 88-92% with a suggestion that the SpO2 be maintained within this range + 2-3%?? We will intermittently collect the SpO2 data from the Pulse Oximeters so we will know the actual ranges. We are going to ask Masimo to develop an even simpler method to download the actual stored values so that this would be very user friendly at the sites. In addition there is a new program that makes analyzing the oximeter data absurdly simple - Its called Profox and RTI could use this to analyze the data and keep the sites blinded.

I am going to begin a final overhaul of the protocol and will incorporate all your suggestions. The Protocol Committee wants to see this version and then would send to the sites with a series of questions.

I have attached a draft that Richard prepared for the sites. This would not go until we revise the protocol. In addition a Table was revised that I had included to further explain the protocol. If we simplify the protocol, I suspect that we would have a much greater chance of buy-in.

The remaining question would be whether DR CPAP without surf is equivalent worse or better than prophylactic surf followed by CPAP after extubation.

I would leave the Verder et al option out of this - ie forced extubation at 10 minutes as these are smaller and more immature infants. We could make the early extubation criteria more vigorous for the larger strata Treatment infants.

Thanks for your input. Please consider all of this. I am going to start the changes and will revise to include Surf for all. I await your responses with breathless anticipation!!

Be well

Neil

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

From: Edward Donovan
To: higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
Sent: Tuesday, August 12, 2003 2:49 PM
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial

Neil,

I have always "thought" of this trial as a trial of a strategy to maintain appropriate lung volume (not too low and not too high) from birth to beyond the period of lung injury risk (2-4 weeks) - compared to "usual care". Unfortunately, there is no such thing as "usual care" which some would say is a major problem in neonatology. In this case, it means that we have to try to define "usual care" which is inherently impossible.

Be that as it may, the "maintenance of appropriate lung volume" strategy has not been tested. While some may argue with the rationale for testing this strategy, I believe that there is sufficient scientific rationale and biologic

plausibility to proceed. What I am most worried about is feasibility of sustaining an intervention that is counter to the way many in the Network practice. We have not succeeded with this in the past. I therefore think we need strong support among the great majority of PIs who will have to "sell" this protocol to their colleagues.
We may have placed too much emphasis on the CPAP component of the intervention, especially the DR CPAP component. It seems to me that this component will not stand alone as the only thing necessary to prevent lung injury. Nor is it clear that the low use of surfactant at Columbia is a central factor in their low incidence of BPD.
I believe that we should emphasize that the intervention is a strategy of respiratory care that optimizes lung volume. I for one believe that this could include liberal use of surfactant (I think this is Option 3, but I'm not sure that I can follow the Tyson-Finer dialogue?).
I agree with Wally that the factorial design is a unique, exciting and doable part of the proposal. Some of our faculty think that the nurses will protest being asked to keep the O2 sat within such narrow limits. I think that their reaction will be more related to the alarm limits rather than the target O2 sat limits.
I don't know if my comments help, but I am certainly not ready to give up on this protocol. BPD is a horrendous problem in our nurseries. We cannot avoid interventional trials to reduce the risk of BPD just because neonatologists don't seem to be able to abandon unproven care. We need to find a way to confront our uncertainty about what is the right way to ventilate these babies.
Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 08/08/2003 7:56:40 PM >>>
Hello All
Please let me know your thoughts re these suggestions. I personally have no interest in Options 1 or 2. VON has been planning their trial for a very long time. Option 2 is designed to produce a difference without addressing the benefit to the control infants they receive neither surf nor CPAP - this will not fly at our IRB.
Option 3 is certainly doable. All infants would get DR surfactant - not current practice in all sites, and avoids early surfactant.
This protocol is now being redesigned by Protocols Committee, and we need to
consider whether the initial protocol was so flawed.
Jon has been very vocal and proliferative in writing almost daily with suggestions. He at first says there is no data to support looking at early CPAP, and feels that the Van Marter paper is of little value, and then indicates that a publication in the Indian Medical journal has better evidence or is useful in defining our approach. Columbia has never prospectively evaluated their data and submitted it for peer review. There are a number of suggestions as noted in our protocol regarding the benefit of CPAP, with almost no-one using it from birth.

This entire process has been onerous and it would appear to me that one individual is determined to see this protocol either scrapped or redesigned to suit their views. We simply do not know if CPAP offers a benefit similar to early/prophylactic surfactant, especially in the era of high ANS use, which was not the case for most if not all of the prophylactic natural surfactant studies. and the opinion of many who are already changing their practice, is that CPAP may be a better intervention.
In addition there is significant opposition to the factorial and the testing of the SpO2 levels, although Rich and others were very supportive.
I am attempting to respond to the committee and will incorporate your views. If you like Option 3 better than our current approach, or at least believe that it may be more doable in the Network, then lets go in that direction. I am not prepared to drop the SpO2 part.
If you like Options 1 or 2, and want to drop the SpO2 portion, let me know that as well. Also, if that is your choice, please step forward to take over this project.
Be well
Neil

----- Original Message -----
From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>; "'Wally Carlo M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Shahnaz Duara'" <sduara@miami.edu>; "'Edward Donovan'" <Edward.Donovan@cchmc.org>; "'Avroy A. Fanaroff M.D.'" <aaf2@po.cwru.edu>; <dale_phelps@urmc.rochester.edu>; <higginsr@mail.nih.gv>; "'Richard Ehrenkranz'" <Richard.Ehrenkranz@yale.edu>; "Michael O'Shea" <moshea@wfubmc.edu>; "Seetha Shankaran (s_shankaran)" <sshankar@med.wayne.edu>
Sent: Friday, August 08, 2003 9:48 AM
Subject: RE: Increasing the feasibility and conclusiveness of the COT trial

> Neil,
>
> Thoughts ref restricting enrollment to infants exposed to antenatal
> steroids: I agree that there are trade-offs, including restricting the
> population in assessing different oxygen saturation goals. However,
> infants not exposed to antenatal steroids are the group for whom the
> benefits of administering prophylactic surfactant are most certain.
> Moreover, it is unclear whether a large proportion infants not exposed
> to steroids would be enrolled as the protocol is now written.
>
> What proportion of this population do you think would be enrolled as the
> study is now designed? What proportion do you think is adequate? The
> proportion of this population enrolled might well be less than 50%,
> perhaps substantially less. Their mean interval between maternal
> admission and delivery would be relatively short, making it particularly
> difficult to enroll these infants because of any delays in NICU or
> research personnel becoming aware that the mother was admitted to L and
> D or because of the time needed to ascertain and verify GA, obtain
> consent, randomize, and arrange for the surfactant and any study
> equipment to be at the bedside. In centers where study personnel would
> be called in to evaluate eligibility and get consent, additional time
> will be required. If in-house NICU personnel are to get consent,

> randomize, and enroll, there will sometimes be delays due to pressing
> clinical demands in the NICU, a problem that may well be greatest in
> centers expected to enroll the greatest number of infants. Obtaining
> consent for the proposed study is likely to be more difficult and time
> consuming than for the pilot because of the inclusion of different
> ventilation criteria and the different oxygen saturation goals and
> because at least in some centers, the delay or reduction in surfactant
> use will be seen as an issue that needs to be discussed. It will be
> difficult to assure that surfactant would be given at 30 minutes if it
> is not given until after NICU admission, because of all the other things
> that happen on admission and perhaps because of a tendency to not obtain
> and warm the surfactant until after a decision is made to administer at
> 30 minutes. For faculty who are concerned about either delaying or
> foregoing surfactant (particularly in the 24-25 weekers) or simply about
> the practical problems of doing the study, the proposal would be an
> easier "sell" if restricted to infants exposed to antenatal steroids.
>
> More thoughts ref the overall design: Whatever is decided about the
> issue discussed above, the current protocol does not assess the
> possibility that DR CPAP/PEEP may improve outcome if surfactant use is
> unaffected but may have no benefit or worsen outcome if CPAP/PEEP
delays
> or reduces use of surfactant. If the study is done as currently
> designed and identifies no benefit or a trend toward a worse outcome in
> the intervention group (as in the pilot), we (and certainly our critics)
> could feel that we did the wrong study. (This would be particularly true
> if other investigators showed that CPAP/PEEP was beneficial when given
> with surfactant). Even we identified benefit were shown, there would
> still be the question of whether greater benefit would be achieved if
> prophylactic surfactant is administered.
>
> In addition, I would think that the Advisory Committee will conclude
> that the current proposal assesses too many interventions in the same
> study.
>
> At the risk of making unwanted suggestions, any of the following design
> modifications could be considered to avoid the above problems:
> a) Assess 3 arms for DR care with one arm given DR CPAP/PEEP and
> prophylactic surfactant (as I understand VON has proposed to do). To
> promote the feasibility of the study, abandon the effort in this study
> to compare to compare different oxygen saturation goals and/or to
> compare conventional and conservative ventilation criteria in the NICU.
> An advantage of this design in the eyes of faculty concerned about
> delaying or reducing surfactant use is that two thirds of the babies
> would receive prophylactic surfactant. The political disadvantage of
> conducting a trial similar to the proposed VON trial is countered by
> such reasons as: 1) We have not stolen the idea for such a trial for an
> important long-standing question. (Indeed, it was suggested by the
> Rochester group in the review of the pilot study); 2) Few important
> questions are resolved in a single trial; 3) The protocol required to
> answer this question will necessarily be quite difficult and the sample
> size of patients who are successfully studied needs to be quite large.
> In this situation, it may be particularly important for there to be at
> least 2 major trials; 4) Our population and question may be somewhat
> different than in VON, (particularly if, despite the complexity of the
> study, we also simultaneously assess either ventilation criteria or
> different oxygen saturation goals).

> b) Assess 2 arms for DR care: CPAP/PEEP plus prophylactic
> surfactant VS no CPAP/PEEP plus prophylactic surfactant and abandon the
> effort to either compare conservative or conventional ventilation
> criteria and/or to compare different oxygen saturation goals. (The
> comparison of CPAP/PEEP plus prophylactic surfactant with no
CPAP/PEEP
> without prophylactic surfactant seems more likely to produce a
> discernible outcome difference than is the proposed comparison of
> CPAP/PEEP without prophylactic surfactant to no CPAP/PEEP plus
> surfactant.) If there is benefit, we or others could proceed to the
> assess CPAP/PEEP without prophylactic surfactant vs. CPAP/PEEP with
> prophylactic surfactant
> c) Abandon the effort to study the DR intervention and randomize
> the infants after admission to simultaneously assess conservative vs.
> traditional ventilation criteria and different oxygen saturation goals.
> This approach would allow us to answer two important and interrelated
> questions. It would also be a simpler and more feasible study than the
> one proposed, it would avoid criticism of copying the VON study, and it
> would avoid it would avoid concerns about delaying or reducing
> surfactant use or misleading conclusions about the potential benefits of
> CPAP/PEEP as described above.
>
> I know that many of you have been thinking about this a long time, and I
> hope this is helpful or at least thought provoking.
>
>
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, August 06, 2003 4:40 PM
> To: Tyson, Jon E
> Cc: higginsr@mail.nih.gov; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara;
> Edward Donovan; Avroy A. Fanaroff, M.D.;
dale_phelps@urmc.rochester.edu;
> higginsr@mail.nih.gv; Richard Ehrenkranz
> Subject: Re: COT trial
>
> Hello Jon
> I think that this is feasible. My question is how such a study would be
> applied to the infants who have not received antenatal steroids. The
> meta
> analyses of any surfactant intervention had variable antenatal steroid
> intervention, and this fact was not even noted in some of the reviewed
> studies. As you are no doubt aware in the Cochrane review of
> prophylactic
> natural surfactant, no study was published after 1991, and before this
> time
> antenatal steroid use was probably less than 20-30%. While I believe
> that we
> could include only women receiving a full course, it will not address a
> significant population who will remain at risk. I am not convinced that
> there is data to suggest that early treatment is inferior to
> prophylaxis,
> considering that prophylaxis treats infants who will do well with no
> treatment. Indeed one of the early surfactant trials began
> administration
> within 5-10 minutes of birth. This area is not nearly so well defined as

> many have thought, as evidenced by the fact that not all Network centers
> use
> prophylactic surfactant treatment.
> I apreciate these thoughts.
> Be well
> Neil
> ----- Original Message -----
> From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
> To: "Neil N Finer" <nfiner@ucsd.edu>
> Cc: "Dale Phelps MD" <dale_phelps@urmc.rochester.edu>; "Rosemary
> Higgins"
> <higginsr@mail.nih.gv>; "Richard Ehrenkranz (richard.ehrenkranz)"
> <richard.ehrenkranz@yale.edu>
> Sent: Wednesday, August 06, 2003 2:01 PM
> Subject: COT trial
>
>
> In struggling to think how the trial would be most successful, I called
> Dale
> today to discuss the protocol. As we mulled it over, she suggested that
> we
> might limit the trial to infants born to mothers who had received
> antenatal
> steroids. If we required 2 doses, this would require the mothers would
> be in
> the hospital for 12 hours. This would reduce my concerns about the
> safety of
> delaying or foregoing surfactant and about the feasibility of enrolling
> a
> high percentage of eligible infants, including concerns about having
> time to
> identify eligible subjects, adequately assess and verify the GA (which
> might
> require sonography), obtain consent, randomize to treatment arms, make
> sure
> that the appropriate equipment was there, and get surfactant to the
> bedside,
> all between admission to L and D and delivery. How does her suggestion
> strike you?
>
> 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: Edward Donovan
To: Higgins, Rosemary (NIH/NICHD); sduara@miami.edu; WCarlo@PEDS.UAB.EDU; aaf2@po.cwru.edu; nfiner@ucsd.edu
Cc: Barbara Warner; Jean Steichen; Vivek Narendran; steichji@ucmail.uc.edu
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial
Date: Wednesday, August 13, 2003 12:43:01 PM

Actually, our center is divided, one hospital with a medical director from our division is very committed to early CPAP even if it means a marked reduction in use of surfactant. Another hospital with another medical director from our division, tends to use early surfactant more aggessively and less CPAP. To me this identifies uncertainty within our division about what is the right thing to do. I believe that this uncertainty will translate into support of a trial.
Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 08/12/2003 7:22:12 PM >>>
Thanks Ed
You are correct - Option #3 from Jon would see all infants get prophylactic surf. I can live with that as I also don't believe that DR CPAP alone is the answer. We need to obtain and maintain FRC - CPAP will help maintain and initial PPV will help obtain FRC. Surfactant will obviate establishing FRC, and if all infants get early surf - we can argue about how early, we can then test the ventilation strategy and see if reducing the duration is crucial to reducing the BPD rate and severity.
It sounds like I should modify the protocol to include early/prophylactic surfactant for all - that would make the initial approach very easy even if it involves a significant change in practice at some centers.
Ed, your center is probably the most aggressive at using early CPAP. Would your group be averse to early surfactant and then aggressively attempting to extubate the Treatment arm?
Would everyone be willing to accept this change, or do you want to try to push the current version ahead.
I am of 2 minds (probably more) - 1) Lets get this study done ASAP with the factorial in a manner acceptable to the majority of sites
2)Lets stick to our guns and see if we can convince the rest of the Network to agree. I suspect that the latter will eat away at our time and enthusiasm. In addition, giving all surf in the DR is consistent with good evidence, and while it will not address the issue of whether early CPAP is as good as early surf, it will allow adequate evaluation of an aggressive weaning strategy and the use of continuing CPAP in the NICU. In our current experience, we are giving DR surf to all less than 27 weeks - we started this after the DR CPAP finished awaiting the next intervention. We do however attempt to the stabilize the infant and the surf is sometimes delayed till 15 minutes or later. However, we are extubating as soon as is possible, and usually by the following morning whenever feasible. The question that would remain - are the 2 arms of the Vent protocol sufficiently distinct?
If we want to move in this direction, what would you all accept as the latest time to give the surfactant - 15 minutes, 30 minutes? I would suggest that we give in the DR < 20 minutes, but could live with the traditional 15 minutes.
You know, the SpO2 will be the easier part of this trial. We need to think about alarm limits and how important they are. Are we going to rigidly specify or merely provide the range ie 88-92% with a suggestion that the SpO2 be maintained within this range + 2-3%?? We will intermittently collect the SpO2 data from the Pulse Oximeters so we will know the actual ranges. We are going to ask Masimo to develop an even simpler method to download the actual stored values so that this would be very user

friendly at the sites. In addition there is a new program that makes analyzing the oximeter data absurdly simple - Its called Profox and RTI could use this to analyze the data and keep the sites blinded.
I am going to begin a final overhaul of the protocol and will incorporate all your suggestions. The Protocol Committee wants to see this version and then would send to the sites with a series of questions.
I have attached a draft that Richard prepared for the sites. This would not go until we revise the protocol. In addition a Table was revised that I had included to further explain the protocol. If we simplify the protocol, I suspect that we would have a much greater chance of buy-in.
The remaining question would be whether DR CPAP without surf is equivalent worse or better than prophylactic surf followed by CPAP after extubation.
I would leave the Verder et al option out of this - ie forced extubation at 10 minutes as these are smaller and more immature infants. We could make the early extubation criteria more vigorous for the larger strata Treatment infants.
Thanks for your input. Please consider all of this. I am going to start the changes and will revise to include Surf for all. I await your responses with breathless anticipation!!
Be well
Neil
----- Original Message -----

From: Edward Donovan
To: higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
Sent: Tuesday, August 12, 2003 2:49 PM
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial

Neil,
I have always "thought" of this trial as a trial of a strategy to maintain appropriate lung volume (not too low and not too high) from birth to beyond the period of lung injury risk (2-4 weeks) - compared to "usual care". Unfortunately, there is no such thing as "usual care" which some would say is a major problem in neonatology. In this case, it means that we have to try to define "usual care" which is inherently impossible.
Be that as it may, the "maintenance of appropriate lung volume" strategy has not been tested. While some may argue with the rationale for testing this strategy, I believe that there is sufficient scientific rationale and biologic plausibility to proceed. What I am most worried about is feasibility of sustaining an intervention that is counter to the way many in the Network practice. We have not succeeded with this in the past. I therefore think we need strong support among the great majority of PIs who will have to "sell" this protocol to their colleagues.
We may have placed too much emphasis on the CPAP component of the intervention, especially the DR CPAP component. It seems to me that this component will not stand alone as the only thing necessary to prevent lung injury. Nor is it clear that the low use of surfactant at Columbia is a central factor in their low incidence of BPD.
I believe that we should emphasize that the intervention is a strategy of respiratory care that optimizes lung volume. I for one believe that this could include liberal use of surfactant (I think this is Option 3, but I'm not sure that I can follow the Tyson-Finer dialogue?).
I agree with Wally that the factorial design is a unique, exciting and doable part of the proposal.
Some of our faculty think that the nurses will protest being asked to keep the O2 sat within such narrow limits. I think that their reaction will be more related to the alarm limits rather than the target O2 sat limits.
I don't know if my comments help, but I am certainly not ready to give up on this protocol. BPD is a horrendous problem in our nurseries. We cannot avoid interventional trials to reduce the risk of BPD just because neonatologists don't seem to be able to abandon unproven care. We need to find a way to confront our uncertainty about what is the right way to ventilate these babies.
Ed

Edward F. Donovan, M.D.
Director
Child Policy Research Center

Children's Hospital Medical Center
3333 Burnet Avenue, ML 7014
Cincinnati, OH 45229-3039
Phone 513-636-0182
Fax 513-636-0171
www.cprc-chmc.uc.edu

>>> "Neil Finer" <nfiner@ucsd.edu> 08/08/2003 7:56:40 PM >>>
Hello All
Please let me know your thoughts re these suggestions. I personally have no interest in Options 1 or 2. VON has been planning their trial for a very long time. Option 2 is designed to produce a difference without addressing the benefit to the control infants they receive neither surf nor CPAP - this will not fly at our IRB.
Option 3 is certainly doable. All infants would get DR surfactant - not current practice in all sites, and avoids early surfactant.
This protocol is now being redesigned by Protocols Committee, and we need to consider whether the initial protocol was so flawed.
Jon has been very vocal and proliferative in writing almost daily with suggestions. He at first says there is no data to support looking at early CPAP, and feels that the Van Marter paper is of little value, and then indicates that a publication in the Indian Medical journal has better evidence or is useful in defining our approach. Columbia has never prospectively evaluated their data and submitted it for peer review. There are a number of suggestions as noted in our protocol regarding the benefit of CPAP, with almost no-one using it from birth.
This entire process has been onerous and it would appear to me that one individual is determined to see this protocol either scrapped or redesigned to suit their views. We simply do not know if CPAP offers a benefit similar to early/prophylactic surfactant, especially in the era of high ANS use, which was not the case for most if not all of the prophylactic natural surfactant studies. and the opinion of many who are already changing their practice, is that CPAP may be a better intervention.
In addition there is significant opposition to the factorial and the testing of the SpO2 levels, although Rich and others were very supportive.
I am attempting to respond to the committee and will incorporate your views.
If you like Option 3 better than our current approach, or at least believe that it may be more doable in the Network, then lets go in that direction. I am not prepared to drop the SpO2 part.
If you like Options 1 or 2, and want to drop the SpO2 portion, let me know that as well. Also, if that is your choice, please step forward to take over this project.
Be well
Neil

----- Original Message -----
From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>; "'Wally Carlo M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Shahnaz Duara'" <sduara@miami.edu>; "'Edward Donovan'" <Edward.Donovan@cchmc.org>; "'Avroy A. Fanaroff M.D.'" <aaf2@po.cwru.edu>; <dale_phelps@urmc.rochester.edu>; <higginsr@mail.nih.gv>; "'Richard Ehrenkranz'" <Richard.Ehrenkranz@yale.edu>; "Michael O'Shea" <moshea@wfubmc.edu>; "Seetha Shankaran (s_shankaran)" <sshankar@med.wayne.edu>
Sent: Friday, August 08, 2003 9:48 AM
Subject: RE: Increasing the feasibility and conclusiveness of the COT trial

> Neil,
>
> Thoughts ref restricting enrollment to infants exposed to antenatal
> steroids: I agree that there are trade-offs, including restricting the
> population in assessing different oxygen saturation goals. However,
> infants not exposed to antenatal steroids are the group for whom the
> benefits of administering prophylactic surfactant are most certain.
> Moreover, it is unclear whether a large proportion infants not exposed
> to steroids would be enrolled as the protocol is now written.
>
> What proportion of this population do you think would be enrolled as the
> study is now designed? What proportion do you think is adequate? The
> proportion of this population enrolled might well be less than 50%,
> perhaps substantially less. Their mean interval between maternal
> admission and delivery would be relatively short, making it particularly
> difficult to enroll these infants because of any delays in NICU or
> research personnel becoming aware that the mother was admitted to L and
> D or because of the time needed to ascertain and verify GA, obtain
> consent, randomize, and arrange for the surfactant and any study
> equipment to be at the bedside. In centers where study personnel would
> be called in to evaluate eligibility and get consent, additional time
> will be required. If in-house NICU personnel are to get consent,
> randomize, and enroll, there will sometimes be delays due to pressing
> clinical demands in the NICU, a problem that may well be greatest in
> centers expected to enroll the greatest number of infants. Obtaining
> consent for the proposed study is likely to be more difficult and time
> consuming than for the pilot because of the inclusion of different
> ventilation criteria and the different oxygen saturation goals and
> because at least in some centers, the delay or reduction in surfactant
> use will be seen as an issue that needs to be discussed. It will be
> difficult to assure that surfactant would be given at 30 minutes if it
> is not given until after NICU admission, because of all the other things
> that happen on admission and perhaps because of a tendency to not obtain
> and warm the surfactant until after a decision is made to administer at
> 30 minutes. For faculty who are concerned about either delaying or
> foregoing surfactant (particularly in the 24-25 weekers) or simply about
> the practical problems of doing the study, the proposal would be an
> easier "sell" if restricted to infants exposed to antenatal steroids.
>
> More thoughts ref the overall design: Whatever is decided about the
> issue discussed above, the current protocol does not assess the
> possibility that DR CPAP/PEEP may improve outcome if surfactant use is
> unaffected but may have no benefit or worsen outcome if CPAP/PEEP delays
> or reduces use of surfactant. If the study is done as currently
> designed and identifies no benefit or a trend toward a worse outcome in
> the intervention group (as in the pilot), we (and certainly our critics)
> could feel that we did the wrong study. (This would be particularly true
> if other investigators showed that CPAP/PEEP was beneficial when given
> with surfactant). Even we identified benefit were shown, there would
> still be the question of whether greater benefit would be achieved if
> prophylactic surfactant is administered.
>
> In addition, I would think that the Advisory Committee will conclude
> that the current proposal assesses too many interventions in the same
> study.

>
> At the risk of making unwanted suggestions, any of the following design
> modifications could be considered to avoid the above problems:
> a) Assess 3 arms for DR care with one arm given DR CPAP/PEEP and
> prophylactic surfactant (as I understand VON has proposed to do). To
> promote the feasibility of the study, abandon the effort in this study
> to compare to compare different oxygen saturation goals and/or to
> compare conventional and conservative ventilation criteria in the NICU.
> An advantage of this design in the eyes of faculty concerned about
> delaying or reducing surfactant use is that two thirds of the babies
> would receive prophylactic surfactant. The political disadvantage of
> conducting a trial similar to the proposed VON trial is countered by
> such reasons as: 1) We have not stolen the idea for such a trial for an
> important long-standing question. (Indeed, it was suggested by the
> Rochester group in the review of the pilot study); 2) Few important
> questions are resolved in a single trial; 3) The protocol required to
> answer this question will necessarily be quite difficult and the sample
> size of patients who are successfully studied needs to be quite large.
> In this situation, it may be particularly important for there to be at
> least 2 major trials; 4) Our population and question may be somewhat
> different than in VON, (particularly if, despite the complexity of the
> study, we also simultaneously assess either ventilation criteria or
> different oxygen saturation goals).
> b) Assess 2 arms for DR care: CPAP/PEEP plus prophylactic
> surfactant VS no CPAP/PEEP plus prophylactic surfactant and abandon the
> effort to either compare conservative or conventional ventilation
> criteria and/or to compare different oxygen saturation goals. (The
> comparison of CPAP/PEEP plus prophylactic surfactant with no CPAP/PEEP
> without prophylactic surfactant seems more likely to produce a
> discernible outcome difference than is the proposed comparison of
> CPAP/PEEP without prophylactic surfactant to no CPAP/PEEP plus
> surfactant.) If there is benefit, we or others could proceed to the
> assess CPAP/PEEP without prophylactic surfactant vs. CPAP/PEEP with
> prophylactic surfactant
> c) Abandon the effort to study the DR intervention and randomize
> the infants after admission to simultaneously assess conservative vs.
> traditional ventilation criteria and different oxygen saturation goals.
> This approach would allow us to answer two important and interrelated
> questions. It would also be a simpler and more feasible study than the
> one proposed, it would avoid criticism of copying the VON study, and it
> would avoid it would avoid concerns about delaying or reducing
> surfactant use or misleading conclusions about the potential benefits of
> CPAP/PEEP as described above.
>
> I know that many of you have been thinking about this a long time, and I
> hope this is helpful or at least thought provoking.
>
>
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, August 06, 2003 4:40 PM
> To: Tyson, Jon E
> Cc: higginsr@mail.nih.gov; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara;
> Edward Donovan; Avroy A. Fanaroff, M.D.; dale_phelps@urmc.rochester.edu;
> higginsr@mail.nih.gv; Richard Ehrenkranz
> Subject: Re: COT trial

>
> Hello Jon
> I think that this is feasible. My question is how such a study would be
> applied to the infants who have not received antenatal steroids. The
> meta
> analyses of any surfactant intervention had variable antenatal steroid
> intervention, and this fact was not even noted in some of the reviewed
> studies. As you are no doubt aware in the Cochrane review of
> prophylactic
> natural surfactant, no study was published after 1991, and before this
> time
> antenatal steroid use was probably less than 20-30%. While I believe
> that we
> could include only women receiving a full course, it will not address a
> significant population who will remain at risk. I am not convinced that
> there is data to suggest that early treatment is inferior to
> prophylaxis,
> considering that prophylaxis treats infants who will do well with no
> treatment. Indeed one of the early surfactant trials began
> administration
> within 5-10 minutes of birth. This area is not nearly so well defined as
> many have thought, as evidenced by the fact that not all Network centers
> use
> prophylactic surfactant treatment.
> I apreciate these thoughts.
> Be well
> Neil
> ----- Original Message -----
> From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
> To: "Neil N Finer" <nfiner@ucsd.edu>
> Cc: "Dale Phelps MD" <dale_phelps@urmc.rochester.edu>; "Rosemary
> Higgins"
> <higginsr@mail.nih.gv>; "Richard Ehrenkranz (richard.ehrenkranz)"
> <richard.ehrenkranz@yale.edu>
> Sent: Wednesday, August 06, 2003 2:01 PM
> Subject: COT trial
>
>
> In struggling to think how the trial would be most successful, I called
> Dale
> today to discuss the protocol. As we mulled it over, she suggested that
> we
> might limit the trial to infants born to mothers who had received
> antenatal
> steroids. If we required 2 doses, this would require the mothers would
> be in
> the hospital for 12 hours. This would reduce my concerns about the
> safety of
> delaying or foregoing surfactant and about the feasibility of enrolling
> a
> high percentage of eligible infants, including concerns about having
> time to
> identify eligible subjects, adequately assess and verify the GA (which
> might
> require sonography), obtain consent, randomize to treatment arms, make
> sure
> that the appropriate equipment was there, and get surfactant to the

> bedside,
> all between admission to L and D and delivery. How does her suggestion
> strike you?
>
> 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: Neil Finer
To: Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial
Date: Tuesday, August 12, 2003 7:21:43 PM
Attachments: COT ltr to PIs draft 6Aug03.doc

Thanks Ed
You are correct - Option #3 from Jon would see all infants get prophylactic surf. I can live with that as I also don't believe that DR CPAP alone is the answer. We need to obtain and maintain FRC - CPAP will help maintain and initial PPV will help obtain FRC. Surfactant will obviate establishing FRC, and if all infants get early surf - we can argue about how early, we can then test the ventilation strategy and see if reducing the duration is crucial to reducing the BPD rate and severity.
It sounds like I should modify the protocol to include early/prophylactic surfactant for all - that would make the initial approach very easy even if it involves a significant change in practice at some centers. Ed, your center is probably the most aggressive at using early CPAP. Would your group be averse to early surfactant and then aggressively attempting to extubate the Treatment arm?
Would everyone be willing to accept this change, or do you want to try to push the current version ahead.
I am of 2 minds (probably more) - 1) Lets get this study done ASAP with the factorial in a manner acceptable to the majority of sites
2)Lets stick to our guns and see if we can convince the rest of the Network to agree. I suspect that the latter will eat away at our time and enthusiasm. In addition, giving all surf in the DR is consistent with good evidence, and while it will not address the issue of whether early CPAP is as good as early surf, it will allow adequate evaluation of an aggressive weaning strategy and the use of continuing CPAP in the NICU. In our current experience, we are giving DR surf to all less than 27 weeks - we started this after the DR CPAP finished awaiting the next intervention. We do however attempt to the stabilize the infant and the surf is sometimes delayed till 15 minutes or later. However, we are extubating as soon as is possible, and usually by the following morning whenever feasible. The question that would remain - are the 2 arms of the Vent protocol sufficiently distinct?
If we want to move in this direction, what would you all accept as the latest time to give the surfactant - 15 minutes, 30 minutes? I would suggest that we give in the DR < 20 minutes, but could live with the traditional 15 minutes.
You know, the SpO2 will be the easier part of this trial. We need to think about alarm limits and how important they are. Are we going to rigidly specify or merely provide the range ie 88-92% with a suggestion that the SpO2 be maintained within this range + 2-3%?? We will intermittently collect the SpO2 data from the Pulse Oximeters so we will know the actual ranges. We are going to ask Masimo to develop an even simpler method to download the actual stored values so that this would be very user friendly at the sites. In addition there is a new program that makes analyzing the oximeter data absurdly simple - Its called Profox and RTI could use this to analyze the data and keep the sites blinded.
I am going to begin a final overhaul of the protocol and will incorporate all your suggestions. The Protocol Committee wants to see this version and then would send to the sites with a series of questions.
I have attached a draft that Richard prepared for the sites. This would not go until we revise the protocol. In addition a Table was revised that I had included to further explain the protocol. If we simplify the protocol, I suspect that we would have a much greater chance of buy-in.
The remaining question would be whether DR CPAP without surf is equivalent worse or better than prophylactic surf followed by CPAP after extubation.
I would leave the Verder et al option out of this - ie forced extubation at 10 minutes as these are smaller and more immature infants. We could make the early extubation criteria more vigorous for the larger strata Treatment infants.
Thanks for your input. Please consider all of this. I am going to start the changes and will revise to include Surf for all. I await your responses with breathless anticipation!!
Be well
Neil
----- Original Message -----

From: Edward Donovan
To: higginsr@mail.nih.gov ; sduara@miami.edu ; WCarlo@PEDS.UAB.EDU ; aaf2@po.cwru.edu ; nfiner@ucsd.edu
Sent: Tuesday, August 12, 2003 2:49 PM
Subject: Re: Fw: Increasing the feasibility and conclusiveness of theCOT trial

Neil,
I have always "thought" of this trial as a trial of a strategy to maintain appropriate lung volume (not too low and not too high) from birth to beyond the period of lung injury risk (2-4 weeks) - compared to "usual care". Unfortunately, there is no such thing as "usual care" which some would say is a major problem in neonatology. In this case, it means that we have to try to define "usual care" which is inherently impossible.
Be that as it may, the "maintenance of appropriate lung volume" strategy has not been tested. While some may argue with the rationale for testing this strategy, I believe that there is sufficient scientific rationale and biologic plausibility to proceed. What I am most worried about is feasibility of sustaining an intervention that is counter to the way many in the Network practice. We have not succeeded with this in the past. I therefore think we need strong support among the great majority of PIs who will have to "sell" this protocol to their colleagues.
We may have placed too much emphasis on the CPAP component of the intervention, especially the DR CPAP component. It seems to me that this component will not stand alone as the only thing necessary to prevent lung injury. Nor is it clear that the low use of surfactant at Columbia is a central factor in their low incidence of BPD.
I believe that we should emphasize that the intervention is a strategy of respiratory care that optimizes lung volume. I for one believe that this could include liberal use of surfactant (I think this is Option 3, but I'm not sure that I can follow the Tyson-Finer dialogue?).
I agree with Wally that the factorial design is a unique, exciting and doable part of the proposal.
Some of our faculty think that the nurses will protest being asked to keep the O2 sat within such narrow limits. I think that their reaction will be more related to the alarm limits rather than the target O2 sat limits.
I don't know if my comments help, but I am certainly not ready to give up on this protocol. BPD is a horrendous problem in our nurseries. We cannot avoid interventional trials to reduce the risk of BPD just because neonatologists don't seem to be able to abandon unproven care. We need to find a way to confront our uncertainty about what is the right way to ventilate these babies.
Ed

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

>>> "Neil Finer" <nfiner@ucsd.edu> 08/08/2003 7:56:40 PM >>>
Hello All
Please let me know your thoughts re these suggestions. I personally have no interest in Options 1 or 2. VON has been planning their trial for a very long time. Option 2 is designed to produce a difference without addressing the benefit to the control infants they receive neither surf nor CPAP - this will not fly at our IRB.
Option 3 is certainly doable. All infants would get DR surfactant - not current practice in all sites, and avoids early surfactant.
This protocol is now being redesigned by Protocols Committee, and we need to consider whether the initial protocol was so flawed.
Jon has been very vocal and proliferative in writing almost daily with

suggestions. He at first says there is no data to support looking at early CPAP, and feels that the Van Marter paper is of little value, and then indicates that a publication in the Indian Medical journal has better evidence or is useful in defining our approach. Columbia has never prospectively evaluated their data and submitted it for peer review. There are a number of suggestions as noted in our protocol regarding the benefit of CPAP, with almost no-one using it from birth.
This entire process has been onerous and it would appear to me that one individual is determined to see this protocol either scrapped or redesigned to suit their views. We simply do not know if CPAP offers a benefit similar to early/prophylactic surfactant, especially in the era of high ANS use, which was not the case for most if not all of the prophylactic natural surfactant studies. and the opinion of many who are already changing their practice, is that CPAP may be a better intervention.
In addition there is significant opposition to the factorial and the testing of the SpO2 levels, although Rich and others were very supportive.
I am attempting to respond to the committee and will incorporate your views. If you like Option 3 better than our current approach, or at least believe that it may be more doable in the Network, then lets go in that direction. I am not prepared to drop the SpO2 part.
If you like Options 1 or 2, and want to drop the SpO2 portion, let me know that as well. Also, if that is your choice, please step forward to take over this project.
Be well
Neil

----- Original Message -----
From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>; "'Wally Carlo M.D.'" <WCarlo@PEDS.UAB.EDU>; "'Shahnaz Duara'" <sduara@miami.edu>; "'Edward Donovan'" <Edward.Donovan@cchmc.org>; "'Avroy A. Fanaroff M.D.'" <aaf2@po.cwru.edu>; <dale_phelps@urmc.rochester.edu>; <higginsr@mail.nih.gv>; "'Richard Ehrenkranz'" <Richard.Ehrenkranz@yale.edu>; "Michael O'Shea" <moshea@wfubmc.edu>; "Seetha Shankaran (s_shankaran)" <sshankar@med.wayne.edu>
Sent: Friday, August 08, 2003 9:48 AM
Subject: RE: Increasing the feasibility and conclusiveness of the COT trial

> Neil,
>
> Thoughts ref restricting enrollment to infants exposed to antenatal
> steroids: I agree that there are trade-offs, including restricting the
> population in assessing different oxygen saturation goals. However,
> infants not exposed to antenatal steroids are the group for whom the
> benefits of administering prophylactic surfactant are most certain.
> Moreover, it is unclear whether a large proportion infants not exposed
> to steroids would be enrolled as the protocol is now written.
>
> What proportion of this population do you think would be enrolled as the
> study is now designed? What proportion do you think is adequate? The
> proportion of this population enrolled might well be less than 50%,
> perhaps substantially less. Their mean interval between maternal
> admission and delivery would be relatively short, making it particularly
> difficult to enroll these infants because of any delays in NICU or
> research personnel becoming aware that the mother was admitted to L and

> D or because of the time needed to ascertain and verify GA, obtain
> consent, randomize, and arrange for the surfactant and any study
> equipment to be at the bedside. In centers where study personnel would
> be called in to evaluate eligibility and get consent, additional time
> will be required. If in-house NICU personnel are to get consent,
> randomize, and enroll, there will sometimes be delays due to pressing
> clinical demands in the NICU, a problem that may well be greatest in
> centers expected to enroll the greatest number of infants. Obtaining
> consent for the proposed study is likely to be more difficult and time
> consuming than for the pilot because of the inclusion of different
> ventilation criteria and the different oxygen saturation goals and
> because at least in some centers, the delay or reduction in surfactant
> use will be seen as an issue that needs to be discussed. It will be
> difficult to assure that surfactant would be given at 30 minutes if it
> is not given until after NICU admission, because of all the other things
> that happen on admission and perhaps because of a tendency to not obtain
> and warm the surfactant until after a decision is made to administer at
> 30 minutes. For faculty who are concerned about either delaying or
> foregoing surfactant (particularly in the 24-25 weekers) or simply about
> the practical problems of doing the study, the proposal would be an
> easier "sell" if restricted to infants exposed to antenatal steroids.
>
> More thoughts ref the overall design: Whatever is decided about the
> issue discussed above, the current protocol does not assess the
> possibility that DR CPAP/PEEP may improve outcome if surfactant use is
> unaffected but may have no benefit or worsen outcome if CPAP/PEEP delays
> or reduces use of surfactant. If the study is done as currently
> designed and identifies no benefit or a trend toward a worse outcome in
> the intervention group (as in the pilot), we (and certainly our critics)
> could feel that we did the wrong study. (This would be particularly true
> if other investigators showed that CPAP/PEEP was beneficial when given
> with surfactant). Even we identified benefit were shown, there would
> still be the question of whether greater benefit would be achieved if
> prophylactic surfactant is administered.
>
> In addition, I would think that the Advisory Committee will conclude
> that the current proposal assesses too many interventions in the same
> study.
>
> At the risk of making unwanted suggestions, any of the following design
> modifications could be considered to avoid the above problems:
> a) Assess 3 arms for DR care with one arm given DR CPAP/PEEP and
> prophylactic surfactant (as I understand VON has proposed to do). To
> promote the feasibility of the study, abandon the effort in this study
> to compare to compare different oxygen saturation goals and/or to
> compare conventional and conservative ventilation criteria in the NICU.
> An advantage of this design in the eyes of faculty concerned about
> delaying or reducing surfactant use is that two thirds of the babies
> would receive prophylactic surfactant. The political disadvantage of
> conducting a trial similar to the proposed VON trial is countered by
> such reasons as: 1) We have not stolen the idea for such a trial for an
> important long-standing question. (Indeed, it was suggested by the
> Rochester group in the review of the pilot study); 2) Few important
> questions are resolved in a single trial; 3) The protocol required to
> answer this question will necessarily be quite difficult and the sample
> size of patients who are successfully studied needs to be quite large.
> In this situation, it may be particularly important for there to be at

> least 2 major trials; 4) Our population and question may be somewhat
> different than in VON, (particularly if, despite the complexity of the
> study, we also simultaneously assess either ventilation criteria or
> different oxygen saturation goals).
> b) Assess 2 arms for DR care: CPAP/PEEP plus prophylactic
> surfactant VS no CPAP/PEEP plus prophylactic surfactant and abandon the
> effort to either compare conservative or conventional ventilation
> criteria and/or to compare different oxygen saturation goals. (The
> comparison of CPAP/PEEP plus prophylactic surfactant with no CPAP/PEEP
> without prophylactic surfactant seems more likely to produce a
> discernible outcome difference than is the proposed comparison of
> CPAP/PEEP without prophylactic surfactant to no CPAP/PEEP plus
> surfactant.) If there is benefit, we or others could proceed to the
> assess CPAP/PEEP without prophylactic surfactant vs. CPAP/PEEP with
> prophylactic surfactant
> c) Abandon the effort to study the DR intervention and randomize
> the infants after admission to simultaneously assess conservative vs.
> traditional ventilation criteria and different oxygen saturation goals.
> This approach would allow us to answer two important and interrelated
> questions. It would also be a simpler and more feasible study than the
> one proposed, it would avoid criticism of copying the VON study, and it
> would avoid it would avoid concerns about delaying or reducing
> surfactant use or misleading conclusions about the potential benefits of
> CPAP/PEEP as described above.
>
> I know that many of you have been thinking about this a long time, and I
> hope this is helpful or at least thought provoking.
>
>
>
> -----Original Message-----
> From: Neil Finer [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, August 06, 2003 4:40 PM
> To: Tyson, Jon E
> Cc: higginsr@mail.nih.gov; Neil Finer; Wally Carlo, M.D.; Shahnaz Duara;
> Edward Donovan; Avroy A. Fanaroff, M.D.; dale_phelps@urmc.rochester.edu;
> higginsr@mail.nih.gv; Richard Ehrenkranz
> Subject: Re: COT trial
>
> Hello Jon
> I think that this is feasible. My question is how such a study would be
> applied to the infants who have not received antenatal steroids. The
> meta
> analyses of any surfactant intervention had variable antenatal steroid
> intervention, and this fact was not even noted in some of the reviewed
> studies. As you are no doubt aware in the Cochrane review of
> prophylactic
> natural surfactant, no study was published after 1991, and before this
> time
> antenatal steroid use was probably less than 20-30%. While I believe
> that we
> could include only women receiving a full course, it will not address a
> significant population who will remain at risk. I am not convinced that
> there is data to suggest that early treatment is inferior to
> prophylaxis,
> considering that prophylaxis treats infants who will do well with no
> treatment. Indeed one of the early surfactant trials began

> administration
> within 5-10 minutes of birth. This area is not nearly so well defined as
> many have thought, as evidenced by the fact that not all Network centers
> use
> prophylactic surfactant treatment.
> I apreciate these thoughts.
> Be well
> Neil
> ----- Original Message -----
> From: "Jon E Tyson" <Jon.E.Tyson@uth.tmc.edu>
> To: "Neil N Finer" <nfiner@ucsd.edu>
> Cc: "Dale Phelps MD" <dale_phelps@urmc.rochester.edu>; "Rosemary
> Higgins"
> <higginsr@mail.nih.gv>; "Richard Ehrenkranz (richard.ehrenkranz)"
> <richard.ehrenkranz@yale.edu>
> Sent: Wednesday, August 06, 2003 2:01 PM
> Subject: COT trial
>
>
> In struggling to think how the trial would be most successful, I called
> Dale
> today to discuss the protocol. As we mulled it over, she suggested that
> we
> might limit the trial to infants born to mothers who had received
> antenatal
> steroids. If we required 2 doses, this would require the mothers would
> be in
> the hospital for 12 hours. This would reduce my concerns about the
> safety of
> delaying or foregoing surfactant and about the feasibility of enrolling
> a
> high percentage of eligible infants, including concerns about having
> time to
> identify eligible subjects, adequately assess and verify the GA (which
> might
> require sonography), obtain consent, randomize to treatment arms, make
> sure
> that the appropriate equipment was there, and get surfactant to the
> bedside,
> all between admission to L and D and delivery. How does her suggestion
> strike you?
>
> 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
>
>
>

DATE: August xx, 2003

TO: NICHD Neonatal Research Network PIs

FROM: Protocol Review Subcommittee
Richard A. Ehrenkranz, MD, Chair; Dale Phelps, MD; Jon Tyson, MD; Mike O'Shea, MD; Neil Finer, MD; Seetha Shankaran, MD; Rosemary Higgins, MD; Ken Poole, PhD

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

Submitted by: Neil Finer for the DR-CPAP Subcommittee

The Protocol Review Subcommittee reviewed this protocol during its conference call on August 4, 2003. Written reviews had been prepared by Jon Tyson, Seetha Shankaran, and Dale Phelps prior to the call. In addition, several members of the subcommittee, especially Jon Tyson, had a dialogue with Neil Finer during the weeks prior to the call. Although Neil is a member of the Subcommittee, he was requested to join the call after about 45 minutes, so that the subcommittee could achieve some consensus about the protocol.

Much of the discussion dealt with the protocol's apparent complexity and whether there were sufficient data to support mounting a large multicenter clinical trial. Specifically, although data exist about the benefit of prophylactic/early surfactant therapy, were their sufficient data to support the treatment arm of the protocol, with the likelihood of not administering surfactant to all these extremely preterm infants. Justification of the factorial design was reviewed. The primary and secondary outcomes and the proposed analytical plan were also reviewed.

The following action plan was developed:

1. Based upon the written protocol reviews and the discussion during the conference call, Neil would make appropriate revisions/edits to the protocol.
2. Ken Poole would review the analytical plan and clarify the sample size and the issue of interaction between the study cells. During the discussion it became clear that we are underpowered to actually look at true interactions, but could evaluate some additive effects.
3. Once the revised protocol was prepared, it would be distributed to the Steering Committee for review at the Network centers. Our goal was to distribute it by the end of August with a several questions to be considered by each PI and his/her colleagues about the protocol.
4. At the September 17-18, 2003 Steering Committee meeting, time would be set aside to review comments and concerns raised at each center. The goal would be to have a relatively final protocol by the time the Steering Committee meeting concludes.

The protocol accompanies this memo as an email attachment. Questions for consideration follow.

1. Does your center think these are important questions that will affect how care of infants will be provided in the future? Specifically,

    a) Does the use of CPAP/PEEP from delivery, along with very conservative indications for mechanical ventilation (more than CPAP and/or Nasal SIMV) improve the rate of survival without BPD?

    b) Does the use of a lower pulse oximtery range result in an improvement in survival without BPD, or of survival without ROP stage 3 or worse?

2. Can we justify withholding prophylactic surfactant (in the delivery room) in those infants ages 26-27 (and maybe 28) weeks who would be assigned to DR CPAP, knowing that if they need more than 50% oxygen at 30 minutes of age that they would be promptly treated? Note: Infants of 24-25 weeks will still get prophylactic surfactant in the DR.

3. Do you think the surfactant studies would have been different for children born > 26 (27, 28) weeks if they had been done in the era of widespread use of antenatal steroids? Do you think some children are "overtreated" with surfactant given the benefits of antenatal steroids?

4. Do you agree with the intubation/extubation criteria as outlined in the study? If not, what would you change? Can your center abide by the intubation and extubation criteria as outlined in the study? Note: they are different, and meant to be so for the two groups.

5. Are you concerned about the addition of a study pulse oximeter to a complex ventilation trial that begins in the delivery room? Note: The infant will be assigned a study oximeter when he/she is randomized at delivery; it needs to be at the NICU bedside by 60 minutes of age. Since the SpO_2 ranges are safe, the values provided by the study oximeter will be utilized as clinical values and caretakers will not need to be concerned about which saturation arm the infant has been assigned to. Furthermore, the study oximeter remains with the infant until he/she is off oxygen and any respiratory support like NCPAP or nasal cannula.

6. Do you think that a difference in the outcomes of "death or BPD" (or "death or stage 3 or worse ROP") from 65% to 55% is an important difference? Should we be able to detect even a smaller difference, like from 65% to 60%?

7. Do you think we should accept a 20% chance of missing a real difference of a 10% absolute decrease in that adverse event rate (power of 80%)? Or do you think we should be at least 90% sure we are not missing a true difference of 10 percentage points% (90% power)?

8. Would your group routinely use caffeine or aminophylline for infants assigned to CPAP instead of ventilators from the delivery room forward? Do you use either of these drugs now for extubation?

From:	Neil Finer
To:	Jon.E.Tyson@uth.tmc.edu
Cc:	Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.
Subject:	DR CPAP critique
Date:	Tuesday, July 22, 2003 8:37:26 PM

Hello Jon

Thank you for your attention to this paper. I have addressed the issues which you have again commented on.

1. The only significant differences noted between the groups were for the blood gases on admission to the NICU

The CPAP infants had a significantly lower pH and higher PaCO2 on admission than the Control infants with a mean and median of 7.21, 7.25, and 54 torr, and 52 torr compared with 7.30, 7.31, and 46torr,and 46 torr for the control infants (p=0.0003, and 0.01). While there were other differences, none, including mortality were different between the groups – CPAP vs CONTROL. I am uncertain as to why we would perform adjusted analyses if there were no univariate differences in outcomes including death, length of ventilation

2. We did not design this trial with any pre-specified stratifications. In addition, the only significant apparent imbalance was the gestational age distribution between the 2 groups, and while there were more infants of 23 weeks in the CPAP arm, these differences were not significant. I have asked RTI to look at the contribution of gestational age etc to death, as this was the only outcome that approached significance with a p=0.07, again not significant.

3. There were no differences in the indications for intubation for surfactant, or the pre-intubation blood gases between the study groups.

4. My response concerning the actual numbers in the revised manuscript was to indicate that these had been corrected and validated by RTI. You did not have the most recent revision.

I am going to use our previous iteration and calculate the feasibility including the Neopuff failures as suggested.

Thanks for your comments

I will separately address your concerns regarding the current protocol.

Regards

Neil Finer

From:	Neil Finer
To:	Richard Ehrenkranz
Cc:	Higgins, Rosemary (NIH/NICHD); Neil Finer; Wally Carlo, M.D.; Shahnaz Duara; Edward Donovan; Avroy A. Fanaroff, M.D.; Jon.E.Tyson@uth.tmc.edu
Subject:	COT Trial - Protocol Review
Date:	Wednesday, July 16, 2003 5:11:57 PM
Attachments:	COT study July 16 03.doc

Hello Richard

I have made 2 additional changes in the COT trial for your review. One was as a result of a question asked by Jon yesterday regrading the justification of the use of surfactant at 30 minutes in treatment infants. I had changed this after I sent you the July 7 draft but did not want to deluge you with many drafts.

I highlighted this change in the accompaning COT revision July 16th for you and Jon and it follows "Infants who receive intubation for resuscitation in the Treatment group may 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 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress..[i][i][ii][ii][iii][iii]

The other change is a result of communication from Ken regarding a question that I had asked at our last Steering meeting prompted by Jons concern. We had discussed whether our sample size was powered to look at the interaction of 2 study maneuvers, and the wording in the July 7th draft reflected their opinion at the time. Ken has now indicated that the wording should be changed to remove the interaction effect, and the sample size is not changed. Thus, we will not necessarily be powered to look at the interaction, but will still address our 2 main hypotheses. Ken feels that this a very reasonable approach

That section now reads "Further analyses has determined that for an effect size of 10% using a Chi-square to detect a difference in proportion among 4 groups would require a sample size of 277 per group for a total 1108 (not adjusted for attrition) will be adequate to provide a test with 80% power. If there is a postulated 15% attrition these numbers increase to 319/group for a total of 1276 infants.

Sorry for these changes. I have sent these to you and Jon only with respect to the Protocols committee.

Be well

Neil

---

[i] Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

[ii] Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

[iii] Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

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

July 3, 2003

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 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 natural surfactant, an intervention 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 precipitated by the 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 where performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SpO2 ranges 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 demonstrated that the early use of CPAP 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]. The use of early CPAP also appears to decrease the need for subsequent surfactant use and mechanical ventilation in premature infants. 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.[6]

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 recommended 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 new technology that can be used to tightly control 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 recommended levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels will 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 [7]. The use of early PEEP improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [8,9]

1.4 Human Experience: Ventilatory Support

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 infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP soon after delivery[10]. 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[11]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[12] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that early use of CPAP was associated with 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.

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.[13] 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[14]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages.

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[15]. 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[16]. 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.[17] 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)[18]. 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[19] 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[20], 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.[21] 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.[22] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[23]

There are currently no studies which have prospectively compared early 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.[24]

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.[25] 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.[262728] 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.[29] 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.[30]

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.[31 32] 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.[33] 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))[34]. 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).[35] 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%).[36] 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 < 1000gm, there was a decrease in the incidence of ROP.[37] 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.[38] A subsequent trial conducted in Australia that compared SpO2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or neurodevelopmental outcome, but resulted in increased duration of oxygen supplementation.[39]

More recently 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.[40] 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.

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.[41] 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[42] 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 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 (≤ 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.

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without 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.

3). We hypothesize that the that relative to infants managed with surfactant and CMV and a high SpO2 range that the combination of early CPAP and a permissive ventilator strategy with a lower SpO2 range will result in increased long term survival without severe

developmental impairment as assessed at 18-22 months corrected age.

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 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 threshold 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 to 27 completed weeks (up to 27 6/7th) 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. 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

Strata: There will be 2 randomization strata, infants of 24 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 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 ventilators 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 (Conventional management with early surfactant) and to either the Low (85%-89%) or High (91% - 95%) SpO2 group. Parents will be approached for consent following admission, 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 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

The randomization to either a high or low SpO2 will be performed immediately following NICU admission, with a maximum allowable delay of 1 hour following NICU admission.

TREATMENT Group

Early CPAP – Treatment Group - Both Strata - 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 and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 7– 8 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.

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 receive intubation for resuscitation in the Treatment group may 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 minutes of birth. This approach is consistent with the previously determined benefit of prophylactic or early surfactant in preterm infants with respiratory distress..[434445] 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.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20 or nasal SIMV.

All non-intubated Treatment infants will be evaluated at 30 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 $\geq$ 90%, they will be immediately intubated and given surfactant. For infants who appear unstable, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SpO2 $\geq$ 90%

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 $\pm$2 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants: ***These infants will treated with a permissive ventilation strategy which will involve the acceptance of higher PaCOs and require higher FiO2 before intervention***

Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated SpO2 ≥ 88% (using the altered Pulse Oximeters)
- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 60 torr with a pH > 7.20,
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

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.

<u>CONTROL Group</u>

<u>NOTE: 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 30 minutes provides a significant survival benefit</u>

<u>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 in the delivery room.</u>

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the delivery room and given surfactant within 30 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in delivery room and given surfactant within 30 minutes of birth, but **MUST** be intubated and receive surfactant if requiring any supplemental Oxygen by 30 minutes.

Intubation Criteria for non-intubated Control infants > 30 minutes of age in 26-27 weeks strata: These Control infants ***MUST*** be intubated and receive surfactant if they meet ***ANY*** of the following criteria:

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 88
- The use of CPAP
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (**Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1**)
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 the centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Protocol for Control infants ensures an evidence based intervention with prophylactic surfactant, and requires intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25
- 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of MAY be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

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 POs 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. 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%.

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 as of June 27th 2003, that this technology is workable.

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

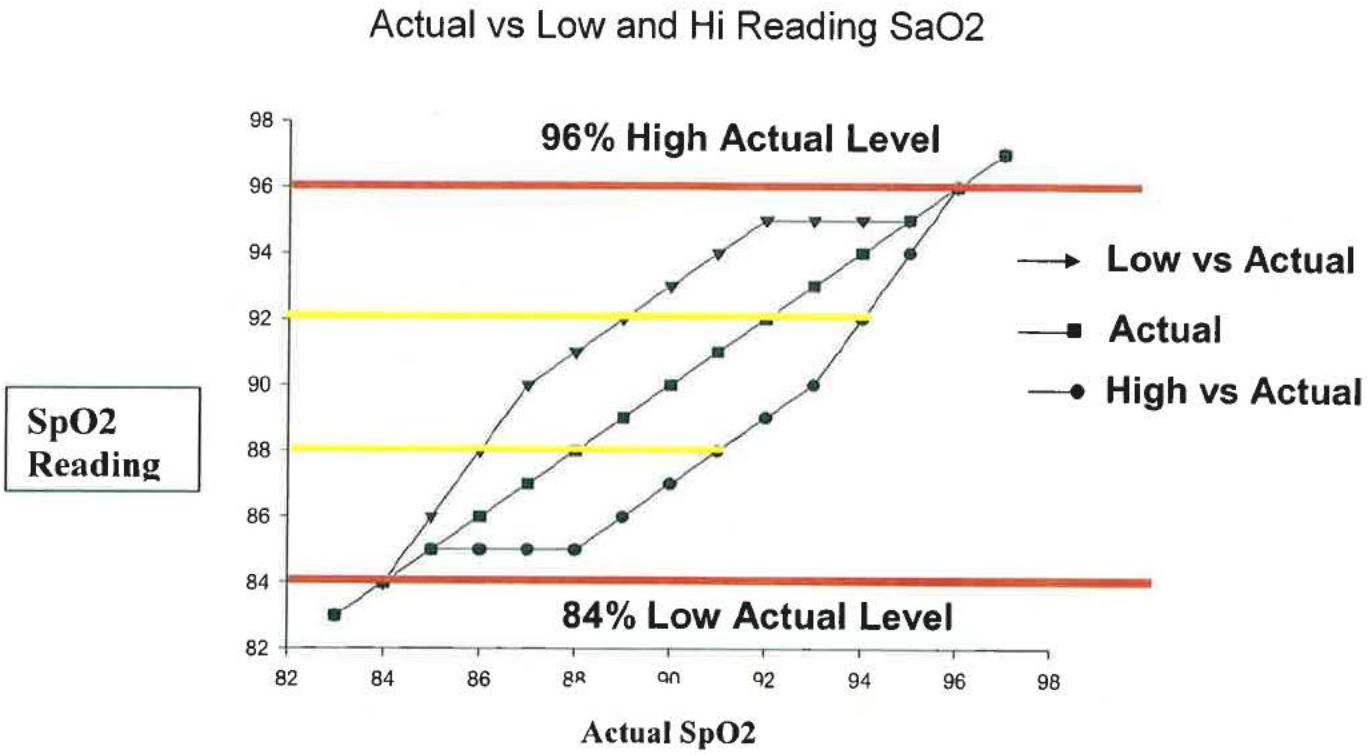
Table. Output and Actual SpO2 Targets and Alarms

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 96%. This will provide for an overall set of limits on actual SpO2 of 84% to 97% 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 96%. 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. 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 the PO SpO2 data was used in the DR CPAP Pilot trial

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.[464748]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants.

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)[49]
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

8.2 Sample Size

As discussed above, there are three main outcomes for the factorial design: mortality or BPD; mortality or ROP; and mortality or NDI. For infants born in 2000, weighing between 401 and 1000 grams and of gestational ages 24-27 weeks, the BPD/mortality and the ROP/mortality rates were 65% and 85%, respectively. 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

Detectable difference in absolute %	Total N1	Total N2
5%	4000	4760
6%	2800	3332
7%	2080	2476
8%	1600	1904
9%	1240	1476
10%	1000	1192
11%	840	1000
12%	700	832
13%	600	716
14%	520	620
15%	448	536

Further analyses has determined that for an effect size of 10% using a Chi-square to detect a difference in proportion among 4 groups would require a sample size of 277 per group for a total 1108 (not adjusted for attrition) will be adequate to provide a test with 80% power. If there is a postulated 15% attrition these numbers increase to 319/group for a total of 1276 infants.

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 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

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

8 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

9 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

10 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.

11 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

12 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

13 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

14 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.

15 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.

16 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.

17 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.

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

19 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.

20 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

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

22 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.

23 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.

24 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.

25 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;

26 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

27 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

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

29 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

30 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

31 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

32 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

33 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

34 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

35 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

36 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.

37 Flynn JT; Bancalari E; Snyder ES; Goldberg RN; Feuer W, and Cassady . A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326

38 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

39 Askie,LA, Henderson-Smart,DJ, Irwig,L, Simpson, JM The Effect of Differing Oxygen Saturation Targeting Ranges on Long Term Growth and Development of Extremely Preterm, Oxygen Dependent Infants: The Boost Trial. .Pediatr Research 2002;45;348A

40 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

41 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

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

43 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

44 Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.

45 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

46 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

47 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 .

48 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

49 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 Ehrenkranz; dale_phelps@urmc.rochester.edu; Jon.E.Tyson@uth.tmc.edu; moshea@wfubmc.edu; sshankar@med.wayne.edu
Cc:	Neil Finer; Higgins, Rosemary (NIH/NICHD); poo@rti.org; petrie@rti.org; Wally Carlo, M.D.; Avroy A. Fanaroff, M.D.; Ed Donovan; Shahnaz Duara
Subject:	Re: Protocols for review
Date:	Friday, June 27, 2003 5:59:47 PM
Attachments:	COT study June 25 03.doc

Hi Richard
I am attaching the current version of the COT protocol. I have added some explanations in Bold to help clarify the manuscript, and added a figure and Table. I have incorporated some of the discussion from the Protocols Committee brief discussions. I look forward to the comments from the committee. I will join the call 45 minutes after it is scheduled. Do we have a time for this call?
Regards
Neil
----- Original Message -----
From: "Richard Ehrenkranz" <Richard.Ehrenkranz@yale.edu>
To: <dale_phelps@urmc.rochester.edu>; <Jon.E.Tyson@uth.tmc.edu>; <moshea@wfubmc.edu>; <nfiner@ucsd.edu>; <sshankar@med.wayne.edu>
Cc: <higginsr@mail.nih.gov>; <poo@rti.org>; <petrie@rti.org>
Sent: Friday, June 27, 2003 10:49 AM
Subject: Protocols for review

> Subcommittee members:
>
> I have attached the inositol protocol submitted by Dale and the antenatal
> steroids - ERCS protocol submitted by Lucky Jain. Neil, Jon and Seetha
> were the primary reviewers of Lucky's protocol in Sept-Oct 2002; his
> response to those reviews and is also attached. I would like Neil, Jon
and
> Seetha to be the primary reviewers of our re-review of that protocol.
>
> I would like Mike and I to be the primary reviewers of Dale's protocol.
Ed
> Donovan has agreed to be the third reviewer of that protocol (I have
> emailed him a copy of that protocol today).
>
> I expect a revised version of the DR CPAP/COT trial within the next few
> days. I would like Dale, Jon and Seetha to be the primary reviewers of
> that protocol.
>
> Carolyn will be screening for potential conference call times and dates.
I
> suggest that the first call review the DR CPAP/COT trial and be scheduled
> for at least an hour. Neil, with your permission, I would prefer you not
> to participate in that call, or perhaps join the call after the first 45
> minutes.
>
> Then we will schedule a 2 hour call in late July or early August for the
> inositol and ANS-ERCS protocols. Dale: we will plan this call so that you
> can join at the end of the discussion of the inositol trial and be on for
> the discussion of the ANS-ERSC trial. Remember, everyone, not just the
> primary reviewers, should read all the protocols.
>
> Thanks for all your work. I think that we should be pleased that we have

> several exciting trials in the pipeline!
>
> Richard

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

June 25, 2003

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 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 natural surfactant, an intervention 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 precipitated by the 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 where performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SaO2 ranges may result in a lower incidence of severe ROP, there is no current agreement on the accepted SaO2 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 demonstrated that the early use of CPAP 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]. The use of early CPAP also appears to decrease the need for subsequent surfactant use and mechanical ventilation in premature infants. 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.[6]

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 recommended 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 new technology that can be used to tightly control 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 recommended levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels will 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 [7]. The use of early PEEP improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury [8,9]

1.4 Human Experience: Ventilatory Support

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 infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP soon after delivery[10]. 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[11]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[12] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that early use of CPAP was associated with 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.

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.[13] 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[14]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages.

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[15]. 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[16]. 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.[17] 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)[18]. 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[19] 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[20], 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 SaO2 > 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.[21] 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.[22] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[23]

There are currently no studies which have prospectively compared early 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.[24]

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.[25] 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.[262728] 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.[29] 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.[30]

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.[31 32] 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.[33] 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))[34]. 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).[35] 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 SaO2 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 SaO2 ranges (88%-98%).[36] They reported that infants who were managed for at least the first 8 weeks of life with SaO_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 SaO_2 ranges. Infants managed with the lower SaO_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 < 1000gm, there was a decrease in the incidence of ROP.[37] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SaO_2 less than 94% to two ranges of SaO_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 SaO_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 CLD.[38] A subsequent trial conducted in Australia that compared SaO_2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not improve survival, growth, or neurodevelopmental outcome, but resulted in increased duration of oxygen supplementation.[39]

More recently 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.[40] 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 SaO2 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 SaO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SaO2 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 SaO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

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.[41] 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[42] 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 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 (see a graphic representation of the two wave forms, Figure 1, in Appendix A). 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 (≤ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SaO_2 range of 85% to 89%) with a higher more conventional SaO_2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

Randomized Intervention	**Low SaO2 85% to 89%**	**High SaO2 91 to 95%**
Early CPAP	Early CPAP + Low SaO2	Early CPAP + High SaO2
Control	Control + Low SaO2	Control + High SaO2

2.2 Primary Hypotheses

1). We hypothesize that that the use of CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without CLD at 36 weeks.

2). We hypothesize that the use of a lower SaO_2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

3). We hypothesize that the combination of early CPAP and a permissive ventilator strategy with a lower SaO_2 range will result in increased long term survival without severe developmental impairment as assessed at 18-22 months corrected age.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SaO_2 range starting at birth in the delivery room will result in the following:

- 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 CLD
- A decreased incidence of CLD at 36 weeks using the physiologic definition of CLD
- A decreased incidence of ROP or threshold 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 to 27 completed weeks (up to 27 6/7th) 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. 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

Strata: There will be 2 randomization strata, infants of 24 to 25 weeks, and infants of 26-27 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 at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery.

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, including disposable circuits, will be provided to all sites for delivery room management. 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 (Conventional management with early surfactant) and to either the Low (85%-89%) or High (91% - 95%) SaO2 group

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 (approximately 32% before discharge and 13% in the first 12 hours based on year 2000 registry data, and will plan for a further 15% attrition.

4.1 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, Treatment infants will be placed on CPAP or PEEP if requiring positive pressure ventilation.

The randomization to either a high or low SaO2 will be performed immediately following NICU admission, with a maximum allowable delay of 1 hour following NICU admission.

TREATMENT Group

Early CPAP – Treatment Group - Both Strata - 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 and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 7– 8 cm cmH_2O. The Neopuff® 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

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 receive intubation for resuscitation in the Treatment group may 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 minutes of birth.[4344] 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.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by nasal prongs using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20.

All non-intubated Treatment infants will be evaluated at 30 minutes of age, and if they require > 50% inspired oxygen to maintain their SaO2 $\geq$ 90%, they will be immediately intubated and given surfactant. For infants who appear unstable, a period of observation of 10-15 minutes may be required to determine the FiO2 necessary to maintain an SaO2 $\geq$ 90%

Intubated Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 hours if criteria listed under Extubation Criteria are met in Treatment infants.

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.

Intubation Criteria for non-intubated Treatment infants:
Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an indicated $SaO_2 \geq 88\%$ (using the altered Pulse Oximeters)
- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock (defined by hypotension, poor perfusion, and acidosis), or the need for surgery

These are 'minimum' criteria meaning that ***intubation may be delayed according to clinician preference, <u>for example</u> a higher FiO_2.***

Intubation performed without meeting any of the above criteria will be considered a study protocol violation.

Extubation Criteria for Intubated Infants in Treatment Group:
Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 60 torr with a pH > 7.20,
- An indicated $SaO_2 \geq 90\%$ 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 (HFO)

These criteria will continue in effect for a minimum of 28 days from birth.

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.

<u>CONTROL Group</u>
<u>NOTE: 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 30 minutes provides a significant survival benefit</u>

Control Group – Delivery Room Management : 24 – 25 weeks Strata Infants will be intubated in the and given surfactant within 30 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants may be intubated in and given surfactant within 30 minutes of birth, but **MUST** be intubated and receive surfactant if requiring supplemental Oxygen by 30 minutes.

Intubation Criteria for non-intubated Control infants in 26-27 weeks strata: These Control infants ***MUST*** be intubated if they meet ***ANY*** of the following criteria:

- An FiO_2 >0.4 to maintain an indicated $SaO_2 \geq 88$
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr (**Note that the average PaCO2 prior to intubation in the DR Feasibility trial was 54 $\pm$ 9.9 torr and the pH**

was 7.3 ± 0.1)

- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

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 the centers. Thus this protocol may result in the intubation of an additional 9% of control infants compared to the current Network experience.

The Protocol for Control infants ensures an evidence based intervention with prophylactic surfactant, and requires intubation at criteria that represent what are considered to be currently acceptable levels of oxygenation and gas exchange.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 50 torr and/or pH > 7.25
- An FiO2 < .40 with a SaO2 > 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Note that we use the wording of MAY be attempted. Clinicians who would wish to continue ventilation for such infants may do so, as is current practice in many centers. There are currently no standard criteria for extubation of such infants.

Study Intervention: Low versus High SaO_2 Range:

There will be 2 ranges of SaO2 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 POs as described below, will display a range of 88% to 92% when the SaO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SaO2 is approximately 86%, and 92% when the actual SaO2 is 89%. Similarly the High range PO will display 88% when the actual SaO2 is 91% and indicate 92% when the actual SaO2 is approximately 94%. See below for further explanation. This deviation I similar to the BOOST trial which used a cotinuius 3% offset. As an added safety feature, the POs used in this trial will gradually revert to the actual SaO2 values and allow the caretakers to be aware of actual SaO2 values < 85% and > 95%.

Low Range Infants:

These infants will be monitored with a target SaO_2 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 SaO2 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 SaO_2 range of 91% -95% with suggested indicated alarm limits of 88% 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 SaO2 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 SaO_2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%.

The suggested alarms limits will be equivalent to 84% to 94% in the low SaO2 group and 86% and 96% in the High group. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed as of June 27th 2003, that this technology is workable.

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

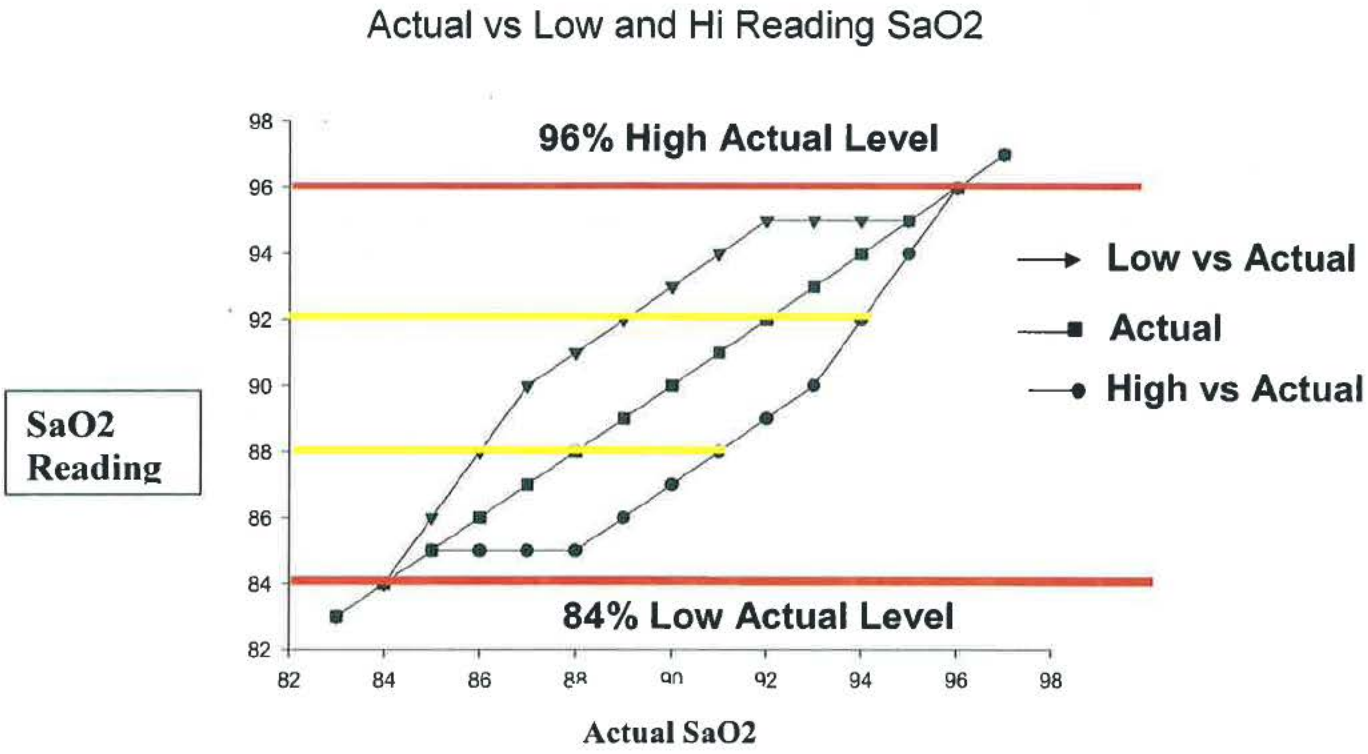
Table. Output and Actual SaO_2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SaO_2 range group	88-92%	85-89%	85-95%	85-94%
High SaO_2 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 SaO2 is below 85% and above 96%. This will provide for an overall set of limits on actual SaO2 of 84% to 97% which we believe will avoid unacceptable levels of hypoxia, ie < 85% and hyperoxia, ie SaO2 > 95%. An infant with an SaO2 outside these limits will have his/her actual SaO2 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 SaO2 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 SaO2s to actual values, as few if any caretakers actually watch the changes in SaO2 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 SaO2 will have, in most circumstances, already occurred. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 96%. Readings below or above these levels will not be altered, and will represent actual SaO2 as determined by the pulse oximeter. Note that the entire range of actual SaO2 is altered to either a lower (Low SaO2 Group) value or higher value

(High SaO2 Group) till the ends of the alarm ranges of 85% and 96% which will ensure that the infants SaO2 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 SaO_2 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. These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SaO2 Group assignments. The technology for downloading the PO SaO2 data was used in the DR CPAP Pilot trial

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®". 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.[454647]. For uniformity nasal SIMV may be used in place of CPAP post extubation, or instead of CPAP in the Treatment Group infants. The maximal set PIP may be no higher than 20 cm H2O. The initial rate shall be no higher than 25 bpm, and the level of PEEP equivalent to the level when using CPAP.

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 SaO_2< 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.
6.

All protocol violations will be sent to the center PI who will discuss 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)[48]
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 CLD or severe ROP

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 CLD at 36 weeks using the physiologic definition of CLD
- 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 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 SaO2 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 studyPOs 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 SaO2) who developed their respective outcome measure (survival without CLD 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

8.2 Sample Size

As discussed above, there are three main outcomes for the factorial design: mortality or CLD; mortality or ROP; and mortality or NDI. For infants born in 2000, weighing between 401 and 1000 grams and of gestational ages 24-27 weeks, the CLD/mortality and the ROP/mortality rates were 65% and 85%, respectively. 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

Detectable difference in absolute %	Total N1	Total N2
5%	4000	4760
6%	2800	3332
7%	2080	2476
8%	1600	1904
9%	1240	1476
10%	1000	1192
11%	840	1000
12%	700	832
13%	600	716
14%	520	620
15%	448	536

Further analyses has determined that for an effect size of 10% including an interaction effect of the same magnitude and using a Chi-square to detect a difference in proportion among 4 groups would require a sample size of 277 per group for a total 1108 (not adjusted for attrition will be adequate to provide a test with 80% power. If there is a postulated 15% attrition these numbers increase to 319/group for a total of 1276 infants.

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 CLD 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(M + SD) Assigned			
Apgar 5 min (M + SD)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)			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, % +SD)			
Other air leaks (N, % +SD)			
CLD at 36 weeks (O_2 dependence)			
CLD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %+SD)			
Number receiving PNS for CLD (N, % +/-SD)			
Alive without neurdevelopmental impairment at 2 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 (%)					
CLD or Death by 36 weeks (%) ±					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
Death by discharge status (%)					
CLD 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 (%)†					
cPVL 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 CLD (%)				
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 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

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

8 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

9 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

10 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.

11 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

12 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

13 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

14 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.

15 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.

16 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.

17 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.

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

19 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.

20 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

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

22 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.

23 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.

24 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.

25 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;

26 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

27 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

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

29 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

30 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

31 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

32 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

33 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

34 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

35 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

36 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.

37 Flynn JT; Bancalari E; Snyder ES; Goldberg RN; Feuer W, and Cassady . A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326

38 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

39 Askie,LA, Henderson-Smart,DJ, Irwig,L, Simpson, JM The Effect of Differing Oxygen Saturation Targeting Ranges on Long Term Growth and Development of Extremely Preterm, Oxygen Dependent Infants: The Boost Trial. .Pediatr Research 2002;45;348A

40 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

41 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

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

43 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

44 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

45 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

46 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 .

47 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

48 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:	Wally Carlo, M.D.
To:	"Neil Finer"; donavan Ed (E-mail); "avroy fanaroff"; Shahnaz Duara; Higgins, Rosemary (NIH/NICHD); "Petrie, Carolyn"
Cc:	Wally Carlo, M.D.
Subject:	FW: Protocol
Date:	Wednesday, June 11, 2003 12:39:55 PM
Attachments:	Definitive Network Trial June 10 03.doc

Dear All:

Enclosed are my comments directly on the draft (in blue) and the most important ones addressed here. I agree with all the highlighted changes unless otherwise stated. I have no major objections as it is.

1) Section 2.2. The ROP outcome should have death as a competing outcome in the current primary hypothesis. I have added ROP only as a secondary. This important as the criticism otherwise could be that we could trade less ROP for more mortality.

2) Section 4.1. Long prong CPAP nose-pieces should also be acceptable.

3) Section 41. I agree with Ed's comments that O_2 sats targets should be specific to those the infant is randomized to. The only exception may have to be in the DR because a generic monitor may have to be used unless we have portable trial pulse oximeters.

I think that oxygenation guidelines should all be based on saturations not on mmHg or torr. I have corrected these throughout the protocol.

4) Sectoin 4.1. Intubation for all in the control groups. It may be justified to intubate and give surfactant to all infants in the control groups, as this procedure would be supported by the meta-analysis addressing this. I think this would be a good way to separate the groups and it is consistent with current practices. We may be criticized for not doing this in the control groups. We should give more thought to this, as this is believed to be the standard of care for many neonatologists. I could go either way on this. I think my group will also.

5) Section 4.1. DR vs 30 min intubation. It is probably preferable to do intubation within 30 minutes rather than in the DR as the former would allow the intubation and subsequent ventilation done in a more controlled environment.

6) Section 4.1. The $PaCO_2$ in intubation and extubation criteria are inconsistent as extubation would be done with a $PaCO_2$ of 55 and intubation with 50.

7) 4.1. SaO_2 alarm ranges. I think it is preferable to have wider alarm limits, as a narrow range will drive the clinicians crazy. Currently, the range is 6% or 7%, depending on which range is used.

I would even prefer a range of 8 or even 10% ;because of masking, alarm ranges around the mean do not alter the mean O_2 sats but would result in wider ranges of saturation values in the babies.

8) Section 4.2. Nasal SIMV. I would not put strict limits on PIP or rate as this is not critical to the trial and not suggested by practice or strong literature.

9) Section 5.3. I think Ken's solution is an excellent one, as we have two interventions but three outcomes. We could also do it as in SAVE with two separate trials using the sample size of the larger trial as the outcomes are different and hopefully not too affected by the other therapy.

Talk to you next week. Wally

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 21, 2003

Delivery Room and Continued Continuous Positive Airway Pressure (CPAP) compared with Prophylactic Surfactant In Extremely Low Birth Weight (ELBW) 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 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 natural surfactant, an intervention 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 precipitated by the 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 where performed during the acute illness. While retrospective cohort studies have suggested that the use of lower SaO2 ranges may result in a lower incidence of severe ROP, there is no current agreement on the accepted SaO2 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 demonstrated that the early use of CPAP 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]. The use of early CPAP also appears to decrease the need for subsequent surfactant use and mechanical ventilation in premature infants. 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.[6]

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 recommended 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 new technology that can be used to tightly control 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 recommended levels.

While prevention of hyperoxia may decrease the risk for ROP and CLD, efforts to maintain lower oxygenation levels will 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[7]. The use of early PEEP improves the response to surfactant, improves lung mechanics increases surfactant pools, and reduces lung injury[8,9]

1.4 Human Experience

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 infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP soon after delivery[10]. 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[11]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[12] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that early use of CPAP was associated with 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.

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.[13] 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[14]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages.

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[15]. 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[16]. 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.[17] 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)[18]. 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[19] 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[20], 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 $SaO2 > 90\%$ 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.[21] 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.[22] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[23]

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.[24] 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.[252627] 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.[28] 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.[29]

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.[30 31] 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.[32] **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)) (Saugstad. Pediatr Res 53:376A, 2003)**. 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).[33] 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 SaO2 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 SaO2 ranges (88%-98%).[34] They reported that infants who were managed for at least the first 8 weeks of life with SaO_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 SaO_2 ranges. Infants managed with the lower SaO_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 < 1000gm, there was a decrease in the incidence of ROP.[35] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SaO_2 less than 94% to two ranges of SaO_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 SaO_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 CLD.[36] A subsequent trial conducted in Australia that compared SaO_2 ranges of 91% - 94% versus 95% - 98% in infants of less than 30 weeks who remained oxygen dependent at 32 weeks reported that additional oxygen supplementation did not **improve survival,** growth, or neurodevelopmental outcome, but resulted in increased duration of oxygen supplementation.[37]

More recently 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.[38] 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 SaO2 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 SaO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SaO2 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 SaO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

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.[39] 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[4041], 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 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 (see a graphic representation of the two wave forms, Figure 1, in Appendix A). 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 (SaO_2 range of 85% to 89%) with a higher more conventional SaO_2 range (92% to 96%) until the infant is no longer requiring ventilatory support or oxygen.

2.2 Primary Hypotheses

1). We hypothesize that that the use of CPAP and a permissive ventilatory strategy begun in the delivery room in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without CLD at 36 weeks.

2). We hypothesize that the use of a lower SaO_2 range (85% to **89**%) will result in **an increase in survival without the** occurrence of ROP or occurrence of threshold ROP (need for surgical intervention). **(Death will be a compelling outcome, so it may be important for the primary hypothesis. ROP can be added as a secondary thesis.)**

3). We hypothesize that the combination of early CPAP and a permissive ventilator strategy with a lower SaO_2 range will result in increased long term survival without severe developmental impairment as assessed at 18-22 months corrected age.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a

permissive ventilator strategy and/or a lower SaO_2 range starting at birth in the delivery room will result in the following:

- 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 CLD
- A decreased incidence of CLD at 36 weeks using the physiologic definition of CLD
- **A decreased incidence of ROP or threshold 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 to 27 completed weeks (up to 27 6/7th) 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. 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

Strata: There will be 2 randomization strata, infants of 24 to 25 weeks, and infants of 26-27 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 infants of 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 at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery.

3.5 Screening Procedures

All admissions for threatened premature delivery may 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, including disposable circuits, will be provided to all sites for delivery room management. 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 either central phone–in randomization or by prepared double-sealed envelopes. Each randomization will indicate randomization to either CPAP and permissive ventilation management and the SaO_2 range, either Low (85%-89%) or High (92% - 96).

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 seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (approximately 32% before discharge and 13% in the first 12 hours based on year 2000 registry data. We will also keep a log of all deliveries below 28 weeks gestation and demographic characteristics of infants not enrolled to determine the percent of infants enrolled.

4.1 Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team.

TREATMENT Group

Early CPAP – Treatment Group - Both Strata - Infants will receive 100% oxygen (or 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 and a face mask. Initial Neopuff settings will be a PIP of 15-25 cm H_2O and a PEEP/CPAP of 7– 8 cm cmH_2O. The Neopuff® 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

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 receive intubation for resuscitation in the Treatment group may 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 minutes of birth.[4243] 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.

Upon NICU admission, all non-intubated Treatment Group infants will be stabilized and placed on nasal CPAP by **prongs (long prongs are used in many centers; I think both short and long prongs should be acceptable)** using either the Bubbleflow or comparable apparatus, with the CPAP being initiated at 7-8 cm H20.

All non-intubated Treatment infants will be evaluated at 30 minutes of age, and if they require > 50% inspired oxygen to maintain the lowest SaO_2 to which they were randomized or a PaO_2 > 45 torr, will be immediately intubated and given surfactant

Treatment infants will be evaluated by the clinicians for immediate extubation to CPAP or nasal SIMV. If immediate extubation is not attempted, extubation ***must be*** attempted within 12 hours if criteria listed under Extubation Criteria are met in Treatment infants.

Intubation Criteria for non-intubated Treatment infants:

Infants ***may*** be intubated in the NICU, and surfactant given, if they meet any of the following criteria.

- An FiO_2 >0.5 to maintain an $SaO_2 \geq 90\%$ or a $PaO_2 \geq 45$ torr Ed has suggested ["to maintain the lowest SaO2 to which they were randomized"?] **(I agree with Ed and delete the PaO_2 as this is an intermittent result, less useful than the continuous O_2 sats)**
- A pH < 7.20 and/or an arterial $PaCO_2$ > 60 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

These are 'minimum' criteria meaning that intubation may be delayed according to clinician preference, for example a higher FiO_2.

Intubation performed without meeting any of the above criteria will be considered a study violation.

Extubation Criteria for Intubated Infants in Early CPAP Group:

Attempt immediate extubation – within 10-60 minutes of intubation for surfactant administration. If unable to extubate immediately because of apnea, or an FiO2 of greater than .5, then extubation ***MUST BE attempted within 12 hours if all of the following criteria are met:***

- $PaCO_2$ < 60 torr with a pH > 7.20,
- An $SaO_2 \geq 88\%$ with an $FiO2 \leq 50\%$ **in the range randomize to within a FiO_2 ≤50%)**
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate < 15 bpm, an

amplitude < 2X MAP if on high frequency ventilation (HFO)
These criteria will continue in effect for a minimum of 28 days from birth.

CONTROL Group

Control Group – Delivery Room Management : 24 – 25 weeks Strata Or Both Strata:(Managing both groups with intubation would separate the groups more. I could go either way. The meta-analysis would support the infants in the 26-27 week stata, and also benefit from prophylactic surfactant) Infants will be intubated in the delivery room given surfactant within 30 minutes of birth.

Control Group – Delivery Room Management : 26 – 27 weeks Strata: If intubated for resuscitation, will receive surfactant within 30 minutes of birth.

All non-intubated Control infants will be evaluated at 30 minutes of age, and if they require > 30% inspired oxygen to maintain an **a saturation in their randomized range**, will be immediately intubated and given surfactant unless other conditions exist which the clinician believes would be contraindications to surfactant such as pneumothorax. Should we simplify this protocol by having all control infants intubated in the DR and given surfactant? This would then result in only requiring extubation criteria for these infants. I will ask RTI for the data for the % of infants > 25 weeks and < 28 weeks that did not require surfactant in the network last year – This may help us to decide this issue Shahnaz would not want this - we can anticipate vigorous objections/issues with protocol violations for intubation of babies without lung disease, which may well be the case in the more mature babies exposed to antenatal steroids. Shahnaz has also asked about increasing the PaCO2 – currently it is above 50 for control infants and > 60 for treatment. This range was as a results of previous suggestions Ed also would rather not have this.

Ed has asked why in the DR?; this forces intubation sometimes by less experienced individuals in a stressful environment. **I prefer intubation by 30 minutes rather than in the DR.**

Intubation Criteria for non-intubated Control infants in 26-27 weeks strata: All Control infants ***MUST*** be intubated if they meet ***ANY*** of the following criteria:

- An FiO_2 >0.4 to maintain an $SaO_2 \geq$ **in the randomized range** using the study pulse oximeters
- A pH < 7.25 and/or an arterial $PaCO_2$ > 50 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or the need for surgery

Non-intubated control infants ***may*** be intubated at lesser criteria at the discretion of the attending physician and following usual unit practice.

Extubation Criteria for Intubated Control Group infants:

Extubation ***MAY*** be attempted if ***ALL*** of the following criteria are present

- $PaCO_2$ < 55 torr **(consider 50 torr because they only need a $PaCO_2$ > 50 for intuation)** and/or pH > 7.25
- An FiO_2 < .40 with a SaO_2 > 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)

These criteria will continue in effect for a minimum of 28 days from birth.

Study Intervention: Low versus High SaO_2 Range:

Low Range Infants:

These infants will be treated with a target SaO_2 range of 85% -89% with alarm limits of 85% and 91%, representing a 6% span for alarms as long as they are receiving any ventilatory support, CPAP, and/or supplemental oxygen. The study pulse oximeters will be utilized in the delivery room and once applied to the infant will remain on the infant and (I like this approach – please comment!) **(Yes, I agree)** 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 standard pulse oximeter will be used.

High Range Infants:

These infants will be treated with a SaO_2 range of 92% -96% with alarm limits of 90% to 96% representing a 6% 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 standard pulse oximeter will be used.

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 SaO_2 (either 85%-89%, or 92%-96%) will be indicated by a range of 88%-92% with alarms set at 87% to 94% in both groups.

These alarms limits will be equivalent to 85% to 91% in the low SaO2 group and 90% and 96% in the High group. Thus this intervention will be blinded to all caretakers.

The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table). The CRT output oxygen saturation alarm limits will also be the same in both groups. In actuality, the low range will have an actual SaO2 of 85% when the reading is 87%, the lower alarm limit for this range. Thus 88% will represent probably 86%. Similarly, for the high range, the actual SaO2 will be 96% when the SaO2 reads 94%, and the actual SaO2 when reading 92% will be approximately 94 to 95%. While this may effectively alter the target range, we believe that the alarm limits in actuality, maintain the desired range.

Table. Output and Actual SaO_2 Targets and Alarms

Wide Target ± 1 Alarm	CRT Output Target	Actual Target	CRT Output Alarms	Actual Alarms
Low SaO_2 range group	88-92%	85-89%	87-94%	85-92%
High SaO_2 range group	88-92%	92-96%	87-94%	**89**-96 %

Neil: Note that the range of the CRT output alarm is 7, but that for the actual alarm is 6. The simplest solution is to decrease the upper limit of the CRT output alarm to 93%. However, I think it is going to be very difficult to keep a range of only 6 in the actual saturation alarms. Clinically many center use alarm ranges of at least 10 (85 to 92% and 89 to 96%). Maybe a range of 7 or even 8 in the alarm limits would be more acceptable to more centers. The CRT output alarm range currently is also 7, so this would be consistent. As mentioned by the Australians in their RCT, the O_2 saturations were distinct due to the masking. Therefore, the alarms can overlap some and still because of regressions to the _____, the saturations in the two groups will differ by slightly less than the mean difference in the ranges (7%).

This alarm range is tighter than those usually used clinically by most centers. The low saturation alarm will prevent hypoxemia (SaO_2 < 85%) in the low SaO_2 range group and hyperoxemia

(SaO_2 > 96%) in the high SaO_2 range group. The average actual SaO_2 targets will be 87 vs 94% in the low vs high SaO_2 range group. The average differences in SaO_2 are comparable to that achieved in the trial by Bancalari et al, using transcutaneous oxygen monitoring.
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 SaO2 is below 85% and above 96%. This will provide for an overall set of limits on actual SaO2 of 84% to 97% which we believe will avoid unacceptable levels of hypoxia, ie < 85% and hyperoxia, ie SaO2>96%. In addition, any infant with an SaO2 outside these limits will have his/her actual SaO2 available for their caretakers to allow appropriate intervention. We have asked the manufacturer to utilize the averaging algorithm of 8 to 16 seconds to allow the change in reading from artificial when within the study ranges to actual when outside these limits. 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 SaO2s to actual values, as few if any caretakers actually watch the changes in SaO2 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 SaO2 will, in most circumstances, have already occurred.

At 3 days and every subsequent 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SaO_2 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.

Eds comments - [I agree with Wally on this. The safety pilot should be built into the trial with specific stopping rules to be applied by an independent DSMB.]This refers to e-mail exchanges that you all received – I hope! The issue was to determine that the altered Pos were providing the ranges specified. I would then suggest that a few centers will initially test these devices to ensure that they are functional. In addition, Post-ROP will also be testing these same devices, but they are going to be very slow in getting started.

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. **(I think we should have a uniform approach till 28 days as mentioned earlier in the protocol)**

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®". 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. **(I would eliminate the rate and PIP restrictions as there are limited data on their certainty)**

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.[444546]. For uniformity nasal SIMV may be used in place of CPAP post extubation, and the maximal set PIP may be no higher than 20 cm H2O. The initial rate shall be no higher than 25 bpm, and the level of PEEP equivalent to the level when using CPAP.

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 SaO_2< 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
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 sent to the center PI who will discuss with the involved clinicians and provide a written summary including steps taken to avoid future violations. (**This is a very good idea)**

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)[47]
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

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 of the combined interventions will be the percentage of infants surviving without CLD or severe ROP. In order to take advantage of a factorial design, all the factors should have the same outcome. Our design currently has 2 factors - ROP for one factor

and CLD for the other factor. Thus we really have two studies done on the same infants. In disussions with Ken this will not allow any sample size savings.

Ken has provided the following thoughts: One way out of this quandary is to consider NDI/death, ROP and CLD as three outcome measures for both treatments (i.e. a 2 X 2 factorial with three outcomes). The down side to this is that it drives up the sample size by having to control the Type I error for three outcomes. This could be helped some by considering NDI/death as a secondary outcome and power the study only for ROP and CLD. If we adopt this approach, then the total sample sizes required for a range of detectable differences are as follows for a 5% level test at 80 % power.

Detectable difference in absolute %	Total N
5%	4000
6%	2800
7%	2080
8%	1600
9%	1240
10%	1000

This would also allow a 10% difference in NDI/death to be detected with a power of 73%. If this looks like a reasonable way to proceed, we can look at other parameters.

I like this approach suggested by Ken, as we have three outcomes of interest while only two interventions, which is unique for a factorial decision.

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 CLD at 36 weeks using the physiologic definition of CLD
- 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 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.

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.

6.1.2 Training of Personnel

The principal investigator of the trial and Fisher-Paykel representatives will train staff during the site visit.

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 (CPAP and saturation ranges) their respective outcome measure (survival without CLD at 36 weeks respectively). The primary analysis will determine if there is an interaction of the interventions on the percent of each infant who survives 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

See Kens comments above We will ask RTI to review the information for the past 2 years regarding the occurrence of intact neurodevelopmental outcomes, death/CLD including the occurrence of CLD using the physiologic definition, and the occurrence of ROP for the gestation groupings of this planned trial, 24-25 weeks, and 26-27 weeks,. We will postulate a significant decrement in death/CLD, approximately 20-30% and determine the sample size required. The information from the feasibility trial will be utilized to determine the following

1. The number of deaths in the feasibility trial to evaluate the power of an analysis for longer-term neurodevelopmental outcomes of survivors.

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 CLD 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

	Early CPAP	Control	P Value
Birth weight (grams) (M + SD)			
Gestation (weeks) (M + SD)			
Apgar 1 min(M + SD) Assigned			
Apgar 5 min (M + SD)Assigned			
Received PPV (Number, %)			
Surfactant in DR (Number, %)			
Received Chest Compression (N%)			
Received Epinephrine (N, %)			

Table 2. Other Outcomes

	Early CPAP	Control	P Value
Total Duration of Mechanical Vent (M+SD)			
% alive off MV by Day 7 (+SD)			
Pneumothoraces (N, % +SD)			
Other air leaks (N, % +SD)			
CLD at 36 weeks (O_2 dependence)			
CLD by Physiologic Definition (N%+SD)			
Survived to discharge (N,% +SD)			
Number Never Intubated (N, %+SD)			
Number receiving PNS for CLD (N, % +/-SD)			
Alive without neurdevelopmental impairment at 2 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 or death by 36 weeks (%)					
Death by 36 weeks (%)					
Threshold ROP in alive infants at 36 weeks (%)					

Table 3. Secondary Outcomes

	Low Saturation	High Saturation	RR	CI	p value
CLD or death by 36 weeks (%)†					
Death by discharge status (%)					
CLD 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 (%)†					
HPVL 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 CLD (%)				
Necrotizing enterocolitis ≥2 (%)				

References

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 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

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

8 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

9 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

10 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.

11 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

12 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

13 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

14 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.

15 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.

16 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.

17 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.

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

19 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.

20 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

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

22 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.

23 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.

24 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;

25 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

26 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

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

28 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

29 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):1296-1299

30 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

31 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

32 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

33 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

34 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.

35 Flynn JT; Bancalari E; Snyder ES; Goldberg RN; Feuer W, and Cassady . A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326

36 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

37 Askie,LA, Henderson-Smart,DJ, Irwig,L, Simpson, JM The Effect of Differing Oxygen Saturation Targeting Ranges on Long Term Growth and Development of Extremely Preterm, Oxygen Dependent Infants: The Boost Trial.Pediatr Research 2002;45;348A

38 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

39 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

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

42 Kendig JW; Ryan RM; SinkinRA; et al. Comparison of two strategies for surfactant prophylaxis in very premature infants: A multicenter randomized trial. Pediatrics 1998;101(6):1006-1012.

43 Walti H; Parisllado J; Breart G, Couchard M. Porcine surfactant replacement therapy in newborns of 25-31 weeks' gestation: A randomized, multicentre trial of prophylaxis versus rescue with multiple low doses. Acta Paediatr 1995;84(8):913-921

44 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

45 - 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 .

46 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

47 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