From: CHMCC Groupwise
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT trial
Date: Tuesday, November 04, 2003 2:37:21 PM

I responded to Neil – I agree with him. At this point, I think we need to get the external reviews, and then recircle with the PI's about the issue of suspending judgment and asking questions. The problem is of course that the PI's only are expressing the concerns of their staff – and we need everyone to run a trial like this.

This will not be easy

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:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	COT Trial
Date:	Thursday, December 04, 2003 2:29:07 PM

Hi Everyone
We had a good conference call yesterday with Alan and Rose. I will prepare a response for you. Essentially we will go back to the original design without the compromises as the external reviewers have critiqued us for these changes. Hopefully the centers will remain interested, but we may lose a few, which may not be bad.
Be well
Neil

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:	COT Trial
Date:	Tuesday, December 09, 2003 4:19:34 PM

Hi Ken
Thanks for the ventilator tables. I need to ask that you provide the number and % of infants of 24 and 25 weeks by site who were intubated and ventilated. We want to ensure that we correctly interpret the tables and that we know what percent at each gestational age were ventilated.
Thanks
Neil

From:	Neil Finer
To:	Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer
Subject:	COT Trial
Date:	Sunday, December 14, 2003 8:13:37 PM
Attachments:	COT Trial Dec 5 03.doc

Hi All
I know that this is a busy time of year. I have not heard from anyone about the revision to the COT Trial that I sent out on Dec 9. I would appreciate any thoughts or comments so that we can send out a final version to the Steering Committee. I have also responded to Masimo and discussed the PO portion with Cynthia Cole.
I look forward to hearing from you. Should I arrange a conference call for Monday or Tuesday?
Be well
Neil

Protocol for the NICHD Neonatal Research Network

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

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 $\geq$ 1100gm, there was a decrease in the incidence of ROP.[47] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO2 less than 94% to two ranges of SpO2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.[48]

Chow et al reported their observations following the institution in 1993 of a detailed oxygen management policy that included strict guidelines in the practices of increasing and weaning of fraction of inspired oxygen (FIO2) and the monitoring of oxygen saturation parameters in the delivery room, during in-house transport of infants to the NICU, and throughout hospitalization.[49] The main objectives were to avoid hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. Their approach was initiated at birth, and included the avoidance of repeated increases and decreases of the FIO2, and a change in previously used alarm limits. They reported that following the implementation of these new management strategies that the incidence of ROP Grades 3 to 4 decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001 and that the need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the last 3 years. They adopted an SpO2 range of 85% to 95% for infants > 32 weeks gestation at birth, and a range of 85% to 93% for infants < 32 weeks. In addition some of their faculty used a range of 83% to 93%. This study did not provide any prospective values of the actual SpO2 ranges that were actually achieved in their infants, and thus it is uncertain whether their observed reductions in ROP were related to the altered SpO2 changes, or to overall changes in management over the period of the study. While these observations are encouraging, the authors did not report the complete neurodevelopmental outcomes for the infants cared for during the period of the new oxygen guidelines, and in the absence of contemporaneous controls, these results cannot be considered as proof that the SpO2 ranges used by this group are beneficial in terms of significant longer -term neurodevelopmental outcomes.

The most recent trial conducted in Australia compared SpO2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.[50] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months.

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.[51] No studies to date have prospectively

randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP[52] using a anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H_2O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

2.1 Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested will be:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (≤ 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 $\geq$ 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.

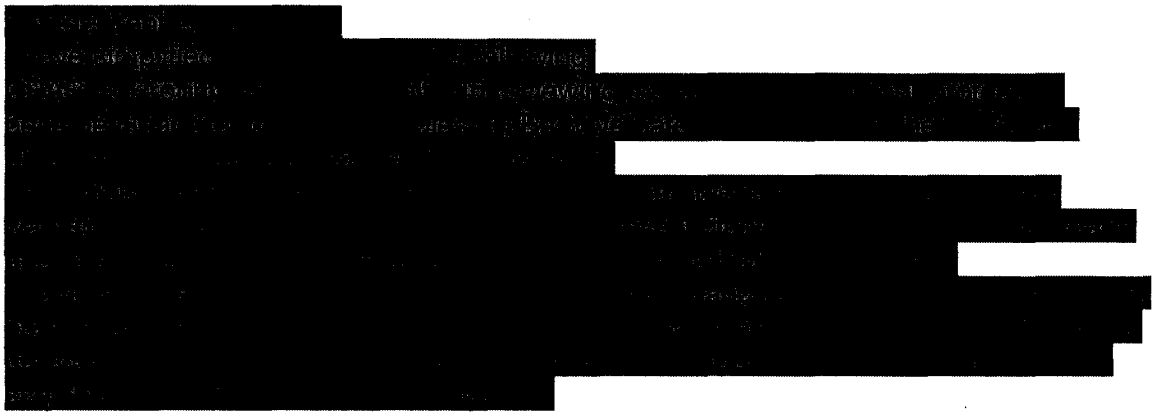
Extubation Criteria for Intubated Infants in Treatment Group: 26 – 27 weeks stratum

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.



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 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 (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.

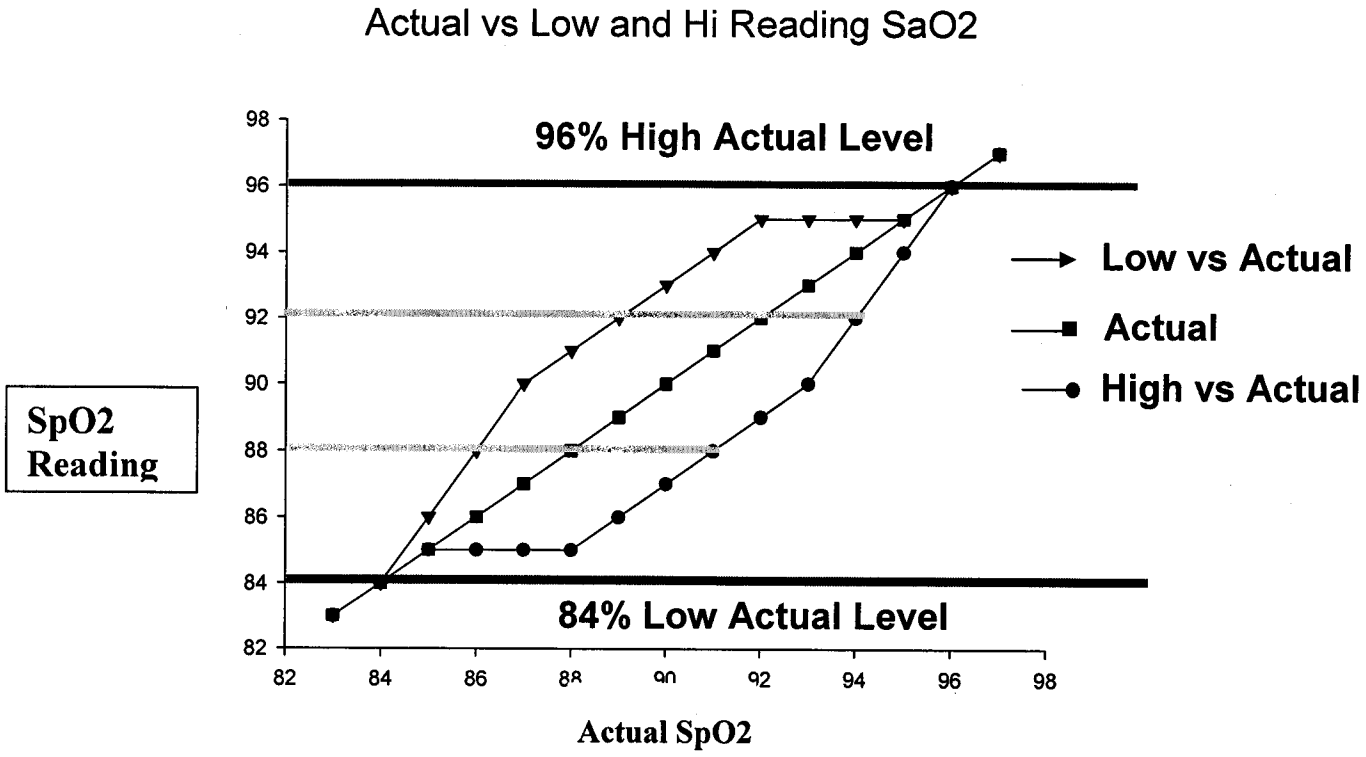
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.


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

At 3 days and every subsequent 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per each second of monitoring for a 72 hour period), from the study pulse oximeters will be downloaded and transmitted without further review or analyses to RTI for subsequent analyses to determine that were are within the desired ranges. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without loosing significant data).These data points will be used to confirm that the infants were managed at the target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

All ventilatory care after 28 days will follow the standard of care for each unit. Each unit will provide guidelines for their approach to continuing mechanical ventilation.

4.2 Delivery of Interventions

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

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.[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: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: DRAFT COT trial
Date: Tuesday, December 16, 2003 11:39:17 AM
Attachments: NRN COT Budget.xls

Rose-

Here is a DRAFT budget. I can come over and explain. I know the N is much larger (1536) than in the protocol but can alter once I speak with 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

1345 infants over a three year period.
COT Trial

	Jan-Nov 2003 GDB	Dec 2003 Est	2003 Est.	40% of GDB	rounded	$2000/pt	of est enrolled 70% survive	rounded
CW	130	12	142	56.8	57	$114,000	39.9	40
TX-Dal	143	13	156	62.4	62	$124,000	43.4	43
WS	215	20	235	94	94	$188,000	65.8	66
MI	258	24	282	112.8	113	$226,000	79.1	79
EM	177	17	194	77.6	78	$156,000	54.6	55
CN	329	30	359	143.6	144	$288,000	100.8	101
IN	271	25	296	118.4	118	$236,000	82.6	83
YL	150	14	164	65.6	66	$132,000	46.2	46
BR	222	21	243	97.2	97	$194,000	67.9	68
ST	122	12	134	53.6	54	$108,000	37.8	38
AL	269	25	294	117.6	118	$236,000	82.6	83
TX-Hstn	303	28	331	132.4	132	$264,000	92.4	92
DU	122	12	134	53.6	54	$108,000	37.8	38
WF	251	23	274	109.6	110	$220,000	77.0	77
NY	116	11	127	50.8	51	$102,000	35.7	36
UCSD	258	24	282	112.8	113	$226,000	79.1	79
					1461	$2,922,000		1024

	$300
FU/pt	
	$12,000
	$12,900
	$19,800
	$23,700
	$16,500
	$30,300
	$24,900
	$13,800
	$20,400
	$11,400
	$24,900
	$27,600
	$11,400
	$23,100
	$10,800
	$23,700
	$307,200

Year 1
COT Trial

	Jan-Nov 2(GDB	Dec 2003 Est	Est. to enroll 1yr.	40% of GDB	rounded	$2000/pt
CW	130	12	142	56.8	57	$114,000
TX-Dal	143	13	156	62.4	62	$124,000
WS	215	20	235	94	94	$188,000
MI	258	24	282	112.8	113	$226,000
EM	177	17	194	77.6	78	$156,000
CN	329	30	359	143.6	144	$288,000
IN	271	25	296	118.4	118	$236,000
YL	150	14	164	65.6	66	$132,000
BR	222	21	243	97.2	97	$194,000
ST	122	12	134	53.6	54	$108,000
AL	269	25	294	117.6	118	$236,000
TX-Hstn	303	28	331	132.4	132	$264,000
DU	122	12	134	53.6	54	$108,000
WF	251	23	274	109.6	110	$220,000
NY	116	11	127	50.8	51	$102,000
UCSD	258	24	282	112.8	113	$226,000
					1461	$2,922,000

Year 2

COT Trial	Enrollment of 6 months in the second year. Est. to enroll 1yr.	Est to enroll 6mo	40% of GDB	$2000/pt	Follow Up begins when study enrollment ends. D of est enrolled 70% survive	$300 FU/pt
CW	142	71	28	$56,000	20	$6,000
TX-Dal	156	78	31	$62,000	22	$6,600
WS	235	118	47	$94,000	33	$9,900
MI	282	141	56	$112,000	40	$12,000
EM	194	97	39	$78,000	27	$8,100
CN	359	180	72	$144,000	50	$15,000
IN	296	148	59	$118,000	41	$12,300
YL	164	82	33	$66,000	23	$6,900
BR	243	123	49	$98,000	34	$10,200
ST	134	67	27	$54,000	19	$5,700
AL	294	147	59	$118,000	41	$12,300
TX-Hstn	331	166	66	$132,000	46	$13,800
DU	134	67	27	$54,000	19	$5,700
WF	274	137	55	$110,000	39	$11,700
NY	127	64	26	$52,000	18	$5,400
UCSD	282	141	56	$112,000	40	$12,000
		1827	730	$1,460,000	512	$153,600

uration of 6 most estimated

1345 infants over a three year period.
COT Trial

	of est enrolled 70% survive	$300 FU/pt
CW	40	$12,000
TX-Dal	43	$12,900
WS	66	$19,800
MI	79	$23,700
EM	55	$16,500
CN	101	$30,300
IN	83	$24,900
YL	46	$13,800
BR	68	$20,400
ST	38	$11,400
AL	83	$24,900
TX-Hstn	92	$27,600
DU	38	$11,400
WF	77	$23,100
NY	36	$10,800
UCSD	79	$23,700
	1024	$307,200

N= 1536

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: DRAFT COT budget
Date: Tuesday, December 16, 2003 2:29:29 PM
Attachments: NRN COT Budget.xls

Here is an updated draft budget. Should we go over this together?

Carolyn Petrie

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

1345 infants over a three year period.
COT Trial

	E	2003 Est.	% of Total	40% of GDB	rounded	#pts per month	rounded	$2000/pt	of est enrolled 80% survive	rounded
CW		142	0.0389	56.8	57	4.75	5	$114,000	45.6	46
TX-Dal		156	0.0428	62.4	62	5.17	5	$124,000	49.6	50
WS		235	0.0644	94	94	7.83	8	$188,000	75.2	75
MI		282	0.0773	112.8	113	9.42	9	$226,000	90.4	90
EM		194	0.0532	77.6	78	6.50	7	$156,000	62.4	62
CN		359	0.0984	143.6	144	12.00	12	$288,000	115.2	115
IN		296	0.0812	118.4	118	9.83	10	$236,000	94.4	94
YL		164	0.045	65.6	66	5.50	6	$132,000	52.8	53
BR		243	0.0666	97.2	97	8.08	8	$194,000	77.6	78
ST		134	0.0367	53.6	54	4.50	5	$108,000	43.2	43
AL		294	0.0806	117.6	118	9.83	10	$236,000	94.4	94
TX-Hstn		331	0.0908	132.4	132	11.00	11	$264,000	105.6	106
DU		134	0.0367	53.6	54	4.50	5	$108,000	43.2	43
WF		274	0.0751	109.6	110	9.17	9	$220,000	88.0	88
NY		127	0.0348	50.8	51	4.25	4	$102,000	40.8	41
UCSD		282	0.0773	112.8	113	9.42	9	$226,000	90.4	90
		3647			1461		123	$2,922,000		1168

estimate that the study recruitment will begin slow and increase as the study progresses. Centers are est. to sta

Estimated costs over 4 year period
$5,140,211

	Training	Equipment					
$300		Pulseox		$2000 per	# of	Neopuff bag	Neo circuit
FU/pt		by size of center		Pulseox	Neopuffbag	$1000 ea	$15/pt
$13,800	$3,500	7.79	8	$16,000	2	$2,000	$855
$15,000	$3,500	8.55	9	$18,000	2	$2,000	$930
$22,500	$3,500	12.89	13	$26,000	3	$3,000	$1,410
$27,000	$3,500	15.46	15	$30,000	4	$4,000	$1,695
$18,600	$3,500	10.64	11	$22,000	3	$3,000	$1,170
$34,500	$3,500	19.69	20	$40,000	4	$4,000	$2,160
$28,200	$3,500	16.23	16	$32,000	4	$4,000	$1,770
$15,900	$3,500	8.99	9	$18,000	2	$2,000	$990
$23,400	$3,500	13.33	13	$26,000	3	$3,000	$1,455
$12,900	$3,500	7.35	7	$14,000	2	$2,000	$810
$28,200	$3,500	16.12	16	$32,000	4	$4,000	$1,770
$31,800	$3,500	18.15	18	$36,000	4	$4,000	$1,980
$12,900	$3,500	7.35	7	$14,000	2	$2,000	$810
$26,400	$3,500	15.03	15	$30,000	3	$3,000	$1,650
$12,300	$3,500	6.96	7	$14,000	2	$2,000	$765
$27,000	$3,500	15.46	16	$32,000	4	$4,000	$1,695
$350,400	$56,000	200.00	200	$400,000	48	$48,000	$21,915

rt at 50% capacityand by the FY05 centers will recruit at full capacity of patient enrollment.

est. cost $3,798,315

FY04 September 2004
COT Trail

	40%GDB est pts enrol/yr	40%GDB est. pts enrol/mo	50% at First mo	$2000/pt	Training	Subtot Indirects	Indirect Rate	***Total Indirect***
CW	57	5	3	$6,000	$3,500	$9,500	0.53	$14,535
TX-Dal	62	5	3	$6,000	$3,500	$9,500	0.495	$14,203
WS	94	8	4	$8,000	$3,500	$11,500	0.56	$17,940
MI	113	9	5	$10,000	$3,500	$13,500	0.5	$20,250
EM	78	7	4	$8,000	$3,500	$11,500	0.515	$17,423
CN	144	12	6	$12,000	$3,500	$15,500	0.545	$23,948
IN	118	10	5	$10,000	$3,500	$13,500	0.53	$20,655
YL	66	6	3	$6,000	$3,500	$9,500	0.49	$14,155
BR	97	8	4	$8,000	$3,500	$11,500	0.299	$14,939
ST	54	5	3	$6,000	$3,500	$9,500	0.393	$13,234
AL	118	10	5	$10,000	$3,500	$13,500	0.6	$21,600
TX-Hstn	132	11	6	$12,000	$3,500	$15,500	0.435	$22,243
DU	54	5	3	$6,000	$3,500	$9,500	0.54	$14,630
WF	110	9	5	$10,000	$3,500	$13,500	0.45	$19,575
NY	51	4	2	$4,000	$3,500	$7,500	0.595	$11,963
UCSD	113	9	5	$10,000	$3,500	$13,500	0.515	$20,453
		123	66	$132,000				$281,742

*# Pulseoxes determined by percentage of expected recruitment by center, calculated on base sheet
**based on number of expected recruitment for entire study

Equipment

Pulseox* by size of center	$2000 per Pulseox	# of Neopuffbag	Neopuff bag $1000 ea	Neo circuit $15/pt**	*Total Direct*	**Total FY04**
8	$16,000	2	$2,000	$855	$18,855	$33,390
9	$18,000	2	$2,000	$930	$20,930	$35,133
13	$26,000	3	$3,000	$1,410	$30,410	$48,350
15	$30,000	4	$4,000	$1,695	$35,695	$55,945
11	$22,000	3	$3,000	$1,170	$26,170	$43,593
20	$40,000	4	$4,000	$2,160	$46,160	$70,108
16	$32,000	4	$4,000	$1,770	$37,770	$58,425
9	$18,000	2	$2,000	$990	$20,990	$35,145
13	$26,000	3	$3,000	$1,455	$30,455	$45,394
7	$14,000	2	$2,000	$810	$16,810	$30,044
16	$32,000	4	$4,000	$1,770	$37,770	$59,370
18	$36,000	4	$4,000	$1,980	$41,980	$64,223
7	$14,000	2	$2,000	$810	$16,810	$31,440
15	$30,000	3	$3,000	$1,650	$34,650	$54,225
7	$14,000	2	$2,000	$765	$16,765	$28,728
16	$32,000	4	$4,000	$1,695	$37,695	$58,148
200	$400,000	48	$48,000	$21,915	$469,915	**$751,657**

FY05 October 2004-September 2005
COT Trial

	40%GDB est pts enrol/yr	#pts est FY05*	$2000/pt	Indirect Rate	**Total FY05**
CW	57	50	$100,000	0.53	$153,000
TX-Dal	62	54	$108,000	0.495	$161,460
WS	94	82	$164,000	0.56	$255,840
MI	113	99	$198,000	0.5	$297,000
EM	78	68	$136,000	0.515	$206,040
CN	144	126	$252,000	0.545	$389,340
IN	118	103	$206,000	0.53	$315,180
YL	66	58	$116,000	0.49	$172,840
BR	97	85	$170,000	0.299	$220,830
ST	54	47	$94,000	0.393	$130,942
AL	118	104	$208,000	0.6	$332,800
TX-Hstn	132	116	$232,000	0.435	$332,920
DU	54	47	$94,000	0.54	$144,760
WF	110	96	$192,000	0.45	$278,400
NY	51	45	$90,000	0.595	$143,550
UCSD	113	99	$198,000	0.515	$299,970
	1461	1279	$2,558,000		**$3,834,872**

N=1345. centers est to recruit 1,279 patients in FY05
*est patient recruitment will end Nov or Dec 2005

FY06 October 2005-September 2006

COT Trial	Starting Mar 06		Pts seen Apr-Sept 06				FU at		**TOTAL**
	Est. First mo*	80% Survivors	est. pts enrol/mo	# seen Apr-Sept	80% Survivors	Total FY06 Survivors	$300/pt	Indirect Rate	**FY06**
CW	3	2	5	30	24	26	$7,800	0.53	$11,934
TX-Dal	3	2	5	30	24	26	$7,800	0.495	$11,661
WS	4	3	8	48	38	41	$12,300	0.56	$19,188
MI	5	4	9	54	43	47	$14,100	0.5	$21,150
EM	4	3	7	42	34	37	$11,100	0.515	$16,817
CN	6	5	12	72	58	63	$18,900	0.545	$29,201
IN	5	4	10	60	48	52	$15,600	0.53	$23,868
YL	3	2	6	36	29	31	$9,300	0.49	$13,857
BR	4	3	8	48	38	41	$12,300	0.299	$15,978
ST	3	2	5	30	24	26	$7,800	0.393	$10,865
AL	5	4	10	60	48	52	$15,600	0.6	$24,960
TX-Hstn	6	5	11	66	53	58	$17,400	0.435	$24,969
DU	3	2	5	30	24	26	$7,800	0.54	$12,012
WF	5	4	9	54	43	47	$14,100	0.45	$20,445
NY	2	2	4	24	19	21	$6,300	0.595	$10,049
UCSD	5	4	9	54	43	47	$14,100	0.515	$21,362
	66		123		590	641	$192,300		**$288,314**

*Expect 80% survival rate. First month's patients are expected in March 2006

FY07 October 2006-March 2007

COT Trial	Pts seen Oct 06-Mar 07				FU at		**TOTAL**
	est. pts enrol/mo	# seen Oct-Mar	80% Survivors	Total FY06 Survivors	$300/pt	Indirect Rate	**FY06**
CW	5	30	24	24	$7,200	0.53	$11,016
TX-Dal	5	30	24	24	$7,200	0.495	$10,764
WS	8	48	38	38	$11,400	0.56	$17,784
MI	9	54	43	43	$12,900	0.5	$19,350
EM	7	42	34	34	$10,200	0.515	$15,453
CN	12	72	58	58	$17,400	0.545	$26,883
IN	10	60	48	48	$14,400	0.53	$22,032
YL	6	36	29	29	$8,700	0.49	$12,963
BR	8	48	38	38	$11,400	0.299	$14,809
ST	5	30	24	24	$7,200	0.393	$10,030
AL	10	60	48	48	$14,400	0.6	$23,040
TX-Hstn	11	66	53	53	$15,900	0.435	$22,817
DU	5	30	24	24	$7,200	0.54	$11,088
WF	9	54	43	43	$12,900	0.45	$18,705
NY	4	24	19	19	$5,700	0.595	$9,092
UCSD	9	54	43	43	$12,900	0.515	$19,544
	123		590	590	$177,000		**$265,368**

*Expect 80% survival rate. First month's patients are expected in March 2006

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: DRAFT COT budget take 3
Date: Tuesday, December 16, 2003 2:54:51 PM
Attachments: NRN COT Budget.xls

Here is the updated one. I am heading over.

Carolyn Petrie

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

1345 infants over a three year period.
COT Trial

	E	2003 Est.	% of Total	40% of GDB	rounded	#pts per month	rounded	$2000/pt	of est enrolled 80% survive	rounded
CW		142	0.0389	56.8	57	4.75	5	$114,000	45.6	46
TX-Dal		156	0.0428	62.4	62	5.17	5	$124,000	49.6	50
WS		235	0.0644	94	94	7.83	8	$188,000	75.2	75
MI		282	0.0773	112.8	113	9.42	9	$226,000	90.4	90
EM		194	0.0532	77.6	78	6.50	7	$156,000	62.4	62
CN		359	0.0984	143.6	144	12.00	12	$288,000	115.2	115
IN		296	0.0812	118.4	118	9.83	10	$236,000	94.4	94
YL		164	0.045	65.6	66	5.50	6	$132,000	52.8	53
BR		243	0.0666	97.2	97	8.08	8	$194,000	77.6	78
ST		134	0.0367	53.6	54	4.50	5	$108,000	43.2	43
AL		294	0.0806	117.6	118	9.83	10	$236,000	94.4	94
TX-Hstn		331	0.0908	132.4	132	11.00	11	$264,000	105.6	106
DU		134	0.0367	53.6	54	4.50	5	$108,000	43.2	43
WF		274	0.0751	109.6	110	9.17	9	$220,000	88.0	88
NY		127	0.0348	50.8	51	4.25	4	$102,000	40.8	41
UCSD		282	0.0773	112.8	113	9.42	9	$226,000	90.4	90
		3647			1461		123	$2,922,000		1168

estimate that the study recruitment will begin slow and increase as the study progresses. Centers are est. to sta

Estimated costs over 4 year period
$5,140,211

	Training	Equipment					
$300 FU/pt		Pulseox by size of center		$2000 per Pulseox	# of Neopuffbag	Neopuff bag $1000 ea	Neo circuit $15/pt
$13,800	$3,500	7.79	8	$16,000	2	$2,000	$855
$15,000	$3,500	8.55	9	$18,000	2	$2,000	$930
$22,500	$3,500	12.89	13	$26,000	3	$3,000	$1,410
$27,000	$3,500	15.46	15	$30,000	4	$4,000	$1,695
$18,600	$3,500	10.64	11	$22,000	3	$3,000	$1,170
$34,500	$3,500	19.69	20	$40,000	4	$4,000	$2,160
$28,200	$3,500	16.23	16	$32,000	4	$4,000	$1,770
$15,900	$3,500	8.99	9	$18,000	2	$2,000	$990
$23,400	$3,500	13.33	13	$26,000	3	$3,000	$1,455
$12,900	$3,500	7.35	7	$14,000	2	$2,000	$810
$28,200	$3,500	16.12	16	$32,000	4	$4,000	$1,770
$31,800	$3,500	18.15	18	$36,000	4	$4,000	$1,980
$12,900	$3,500	7.35	7	$14,000	2	$2,000	$810
$26,400	$3,500	15.03	15	$30,000	3	$3,000	$1,650
$12,300	$3,500	6.96	7	$14,000	2	$2,000	$765
$27,000	$3,500	15.46	16	$32,000	4	$4,000	$1,695
$350,400	$56,000	200.00	200	$400,000	48	$48,000	$21,915

rt at 50% capacityand by the FY05 centers will recruit at full capacity of patient enrollment.

est. cost $3,798,315

FY04 September 2004
COT Trail

	40%GDB est pts enrol/yr	40%GDB est. pts enrol/mo	50% at First mo	$2000/pt	Training	Subtot Indirects	Indirect Rate	***Total Indirect***
CW	57	5	3	$6,000	$3,500	$9,500	0.53	$14,535
TX-Dal	62	5	3	$6,000	$3,500	$9,500	0.495	$14,203
WS	94	8	4	$8,000	$3,500	$11,500	0.56	$17,940
MI	113	9	5	$10,000	$3,500	$13,500	0.5	$20,250
EM	78	7	4	$8,000	$3,500	$11,500	0.515	$17,423
CN	144	12	6	$12,000	$3,500	$15,500	0.545	$23,948
IN	118	10	5	$10,000	$3,500	$13,500	0.53	$20,655
YL	66	6	3	$6,000	$3,500	$9,500	0.49	$14,155
BR	97	8	4	$8,000	$3,500	$11,500	0.299	$14,939
ST	54	5	3	$6,000	$3,500	$9,500	0.393	$13,234
AL	118	10	5	$10,000	$3,500	$13,500	0.6	$21,600
TX-Hstn	132	11	6	$12,000	$3,500	$15,500	0.435	$22,243
DU	54	5	3	$6,000	$3,500	$9,500	0.54	$14,630
WF	110	9	5	$10,000	$3,500	$13,500	0.45	$19,575
NY	51	4	2	$4,000	$3,500	$7,500	0.595	$11,963
UCSD	113	9	5	$10,000	$3,500	$13,500	0.515	$20,453
		123	66	$132,000				$281,742

*# Pulseoxes determined by percentage of expected recruitment by center, calculated on base sheet
**based on number of expected recruitment for entire study

Equipment						
Pulseox* by size of center	$2000 per Pulseox	# of Neopuffbag	Neopuff bag $1000 ea	Neo circuit $15/pt**	***Total Direct***	**Total FY04**
8	$16,000	2	$2,000	$855	$18,855	$33,390
9	$18,000	2	$2,000	$930	$20,930	$35,133
13	$26,000	3	$3,000	$1,410	$30,410	$48,350
15	$30,000	4	$4,000	$1,695	$35,695	$55,945
11	$22,000	3	$3,000	$1,170	$26,170	$43,593
20	$40,000	4	$4,000	$2,160	$46,160	$70,108
16	$32,000	4	$4,000	$1,770	$37,770	$58,425
9	$18,000	2	$2,000	$990	$20,990	$35,145
13	$26,000	3	$3,000	$1,455	$30,455	$45,394
7	$14,000	2	$2,000	$810	$16,810	$30,044
16	$32,000	4	$4,000	$1,770	$37,770	$59,370
18	$36,000	4	$4,000	$1,980	$41,980	$64,223
7	$14,000	2	$2,000	$810	$16,810	$31,440
15	$30,000	3	$3,000	$1,650	$34,650	$54,225
7	$14,000	2	$2,000	$765	$16,765	$28,728
16	$32,000	4	$4,000	$1,695	$37,695	$58,148
200	$400,000	48	$48,000	$21,915	$469,915	**$751,657**

FY05 October 2004-September 2005
COT Trial

	40%GDB est pts enrol/yr	#pts est FY05*	$2000/pt	Indirect Rate	**Total FY05**
CW	57	50	$100,000	0.53	$153,000
TX-Dal	62	54	$108,000	0.495	$161,460
WS	94	82	$164,000	0.56	$255,840
MI	113	99	$198,000	0.5	$297,000
EM	78	68	$136,000	0.515	$206,040
CN	144	126	$252,000	0.545	$389,340
IN	118	103	$206,000	0.53	$315,180
YL	66	58	$116,000	0.49	$172,840
BR	97	85	$170,000	0.299	$220,830
ST	54	47	$94,000	0.393	$130,942
AL	118	104	$208,000	0.6	$332,800
TX-Hstn	132	116	$232,000	0.435	$332,920
DU	54	47	$94,000	0.54	$144,760
WF	110	96	$192,000	0.45	$278,400
NY	51	45	$90,000	0.595	$143,550
UCSD	113	99	$198,000	0.515	$299,970
	1461	1279	$2,558,000		**$3,834,872**

N=1345. centers est to recruit 1,279 patients in FY05
*est patient recruitment will end Nov or Dec 2005

FY06 October 2005-September 2006

COT Trial	Starting Mar 06		Pts seen Apr-Sept 06				FU at		TOTAL
	Est. First mo*	80% Survivors	est. pts enrol/mo	# seen Apr-Sept	80% Survivors	Total FY06 Survivors	$300/pt	Indirect Rate	**FY06**
CW	3	2	5	30	24	26	$7,800	0.53	$11,934
TX-Dal	3	2	5	30	24	26	$7,800	0.495	$11,661
WS	4	3	8	48	38	41	$12,300	0.56	$19,188
MI	5	4	9	54	43	47	$14,100	0.5	$21,150
EM	4	3	7	42	34	37	$11,100	0.515	$16,817
CN	6	5	12	72	58	63	$18,900	0.545	$29,201
IN	5	4	10	60	48	52	$15,600	0.53	$23,868
YL	3	2	6	36	29	31	$9,300	0.49	$13,857
BR	4	3	8	48	38	41	$12,300	0.299	$15,978
ST	3	2	5	30	24	26	$7,800	0.393	$10,865
AL	5	4	10	60	48	52	$15,600	0.6	$24,960
TX-Hstn	6	5	11	66	53	58	$17,400	0.435	$24,969
DU	3	2	5	30	24	26	$7,800	0.54	$12,012
WF	5	4	9	54	43	47	$14,100	0.45	$20,445
NY	2	2	4	24	19	21	$6,300	0.595	$10,049
UCSD	5	4	9	54	43	47	$14,100	0.515	$21,362
	66		123		590	641	$192,300		**$288,314**

*Expect 80% survival rate. First month's patients are expected in March 2006

FY07 October 2006-March 2007

COT Trial	Pts seen Oct 06-Mar 07				FU at		**TOTAL**
	est. pts enrol/mo	# seen Oct-Mar	80% Survivors	Total FY06 Survivors	$300/pt	Indirect Rate	**FY06**
CW	5	30	24	24	$7,200	0.53	$11,016
TX-Dal	5	30	24	24	$7,200	0.495	$10,764
WS	8	48	38	38	$11,400	0.56	$17,784
MI	9	54	43	43	$12,900	0.5	$19,350
EM	7	42	34	34	$10,200	0.515	$15,453
CN	12	72	58	58	$17,400	0.545	$26,883
IN	10	60	48	48	$14,400	0.53	$22,032
YL	6	36	29	29	$8,700	0.49	$12,963
BR	8	48	38	38	$11,400	0.299	$14,809
ST	5	30	24	24	$7,200	0.393	$10,030
AL	10	60	48	48	$14,400	0.6	$23,040
TX-Hstn	11	66	53	53	$15,900	0.435	$22,817
DU	5	30	24	24	$7,200	0.54	$11,088
WF	9	54	43	43	$12,900	0.45	$18,705
NY	4	24	19	19	$5,700	0.595	$9,092
UCSD	9	54	43	43	$12,900	0.515	$19,544
	123		590	590	$177,000		**$265,368**

*Expect 80% survival rate. First month's patients are expected in March 2006

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT budget
Date: Thursday, December 18, 2003 11:45:59 AM
Attachments: NRN COT Budget.xls

Here it is!!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 18, 2003 11:24 AM
To: 'Petrie, Carolyn'
Subject: RE: COT budget

Fine
Sed it when you have it. Also PPB meeting at 12 noon today. I brought in some lemon cake
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, December 18, 2003 11:22 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT budget

Rose-

I will change est. # of GDB babies to 25%. If we expect about 40% GDB to be eligible, and from Preemie, expect to enroll about 60%, therefore 25% of GDB babies will enter the study. This will actually spread over three years.

Carolyn Petrie

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

FY08 October 2007

COT Trial	Pts seen Oct 07 est. pts enrol/mo	80% Survivors	FU at $300/pt	Indirect Rate	**TOTAL FY08**
CW	3	2	$600	0.53	$918
TX-Dal	3	2	$600	0.495	$897
WS	5	4	$1,200	0.56	$1,872
MI	6	5	$1,500	0.5	$2,250
EM	4	3	$900	0.515	$1,364
CN	8	7	$2,100	0.545	$3,245
IN	6	5	$1,500	0.53	$2,295
YL	3	2	$600	0.49	$894
BR	5	4	$1,200	0.299	$1,559
ST	3	2	$600	0.393	$836
AL	6	5	$1,500	0.6	$2,400
TX-Hstn	7	6	$1,800	0.435	$2,583
DU	3	2	$600	0.54	$924
WF	6	5	$1,500	0.45	$2,175
NY	3	2	$600	0.595	$957
UCSD	6	5	$1,500	0.515	$2,273
	77	61	$18,300		**$27,440**

*Expect 80% survival rate.

FY07 October 2006-September 2007

COT Trial	Pts seen Oct 06-Sept est. pts enrol/yr	80% Survivors	FU at $300/pt	Indirect Rate	**TOTAL FY07**
CW	36	29	$8,700	0.53	$13,311
TX-Dal	39	31	$9,300	0.495	$13,904
WS	59	47	$14,100	0.56	$21,996
MI	71	57	$17,100	0.5	$25,650
EM	49	39	$11,700	0.515	$17,726
CN	90	72	$21,600	0.545	$33,372
IN	74	59	$17,700	0.53	$27,081
YL	41	33	$9,900	0.49	$14,751
BR	61	49	$14,700	0.299	$19,095
ST	34	27	$8,100	0.393	$11,283
AL	74	59	$17,700	0.6	$28,320
TX-Hstn	83	66	$19,800	0.435	$28,413
DU	34	27	$8,100	0.54	$12,474
WF	69	55	$16,500	0.45	$23,925
NY	32	26	$7,800	0.595	$12,441
UCSD	71	57	$17,100	0.515	$25,907
	917	733	$219,900		**$329,648**

*Expect 80% survival rate. First month's patients are expected in March 2006

FY06 October 2005-September 2006

COT Trial	25%GDB est pts enrol/yr	to complete enrollment	$2000/pt	Starting Mar 06 Est. First mo*	80% Survivors	Pts seen Apr-Sept 06 est. pts enrol/mo	# seen Apr-Sept	80% Survivors
CW	36	15	$30,000	2	2	3	18	14
TX-Dal	39	16	$32,000	2	2	3	18	14
WS	59	25	$50,000	3	2	5	30	24
MI	71	30	$60,000	3	2	6	36	29
EM	49	21	$42,000	2	2	4	24	19
CN	90	38	$76,000	4	3	8	48	38
IN	74	31	$62,000	3	2	6	36	29
YL	41	17	$34,000	2	2	3	18	14
BR	61	26	$52,000	3	2	5	30	24
ST	34	14	$28,000	2	2	3	18	14
AL	74	31	$62,000	3	2	6	36	29
TX-Hstn	83	35	$70,000	4	3	7	42	34
DU	34	14	$28,000	2	2	3	18	14
WF	69	29	$58,000	3	2	6	36	29
NY	32	13	$26,000	2	2	3	18	14
UCSD	71	30	$60,000	3	2	6	36	29
	917	385	$770,000	43		77		368

385 remaining for FY06 enrollment

*Expect 80% survival rate. First month's patients are expected in March 2006. Enrollments est to end Ma

Total FY06 Survivors	FU at $300/pt	Indirect Rate	Indirect Cost	**TOTAL FY06**
16	$4,800	0.53	$18,444	$53,244
16	$4,800	0.495	$18,216	$55,016
26	$7,800	0.56	$32,368	$90,168
31	$9,300	0.5	$34,650	$103,950
21	$6,300	0.515	$24,875	$73,175
41	$12,300	0.545	$48,124	$136,424
31	$9,300	0.53	$37,789	$109,089
16	$4,800	0.49	$19,012	$57,812
26	$7,800	0.299	$17,880	$77,680
16	$4,800	0.393	$12,890	$45,690
31	$9,300	0.6	$42,780	$114,080
37	$11,100	0.435	$35,279	$116,379
16	$4,800	0.54	$17,712	$50,512
31	$9,300	0.45	$30,285	$97,585
16	$4,800	0.595	$18,326	$49,126
31	$9,300	0.515	$35,690	$104,990
402	$120,600			**$1,334,919**

ay 06

FY05 October 2004-September 2005
COT Trial

	25%GDB est pts enrol/yr	$2000/pt	Indirect Rate	**Total FY05**
CW	36	$72,000	0.53	$110,160
TX-Dal	39	$78,000	0.495	$116,610
WS	59	$118,000	0.56	$184,080
MI	71	$142,000	0.5	$213,000
EM	49	$98,000	0.515	$148,470
CN	90	$180,000	0.545	$278,100
IN	74	$148,000	0.53	$226,440
YL	41	$82,000	0.49	$122,180
BR	61	$122,000	0.299	$158,478
ST	34	$68,000	0.393	$94,724
AL	74	$148,000	0.6	$236,800
TX-Hstn	83	$166,000	0.435	$238,210
DU	34	$68,000	0.54	$104,720
WF	69	$138,000	0.45	$200,100
NY	32	$64,000	0.595	$102,080
UCSD	71	$142,000	0.515	$215,130
	917	$1,834,000		**$2,749,282**

N=1345. est. 43 in FY04, there remain 1,302 patients

FY04 September 2004
COT Trail

	25%GDB est pts enrol/yr	25%GDB est. pts enrol/mo	50% at First mo	$2000/pt	Training	Subtot Indirects	Indirect Rate	***Total Indirect***
CW	36	3	2	$4,000	$3,500	$7,500	0.53	$11,475
TX-Dal	39	3	2	$4,000	$3,500	$7,500	0.495	$11,213
WS	59	5	3	$6,000	$3,500	$9,500	0.56	$14,820
MI	71	6	3	$6,000	$3,500	$9,500	0.5	$14,250
EM	49	4	2	$4,000	$3,500	$7,500	0.515	$11,363
CN	90	8	4	$8,000	$3,500	$11,500	0.545	$17,768
IN	74	6	3	$6,000	$3,500	$9,500	0.53	$14,535
YL	41	3	2	$4,000	$3,500	$7,500	0.49	$11,175
BR	61	5	3	$6,000	$3,500	$9,500	0.299	$12,341
ST	34	3	2	$4,000	$3,500	$7,500	0.393	$10,448
AL	74	6	3	$6,000	$3,500	$9,500	0.6	$15,200
TX-Hstn	83	7	4	$8,000	$3,500	$11,500	0.435	$16,503
DU	34	3	2	$4,000	$3,500	$7,500	0.54	$11,550
WF	69	6	3	$6,000	$3,500	$9,500	0.45	$13,775
NY	32	3	2	$4,000	$3,500	$7,500	0.595	$11,963
UCSD	71	6	3	$6,000	$3,500	$9,500	0.515	$14,393
		77	43	$86,000				$212,768

*# Pulseoxes determined by percentage of expected recruitment by center, calculated on base sheet
**based on number of expected recruitment for entire study

Equipment						
Pulseox* by size of center	$2000 per Pulseox	# of Neopuffbag	Neopuff bag $1000 ea	Neo circuit $15/pt**	***Total Direct***	**Total FY04**
8	$16,000	2	$2,000	$885	$18,885	$30,360
9	$18,000	2	$2,000	$975	$20,975	$32,188
13	$26,000	3	$3,000	$1,455	$30,455	$45,275
15	$30,000	4	$4,000	$1,740	$35,740	$49,990
11	$22,000	3	$3,000	$1,200	$26,200	$37,563
20	$40,000	4	$4,000	$2,220	$46,220	$63,988
16	$32,000	4	$4,000	$1,830	$37,830	$52,365
9	$18,000	2	$2,000	$1,020	$21,020	$32,195
13	$26,000	3	$3,000	$1,500	$30,500	$42,841
7	$14,000	2	$2,000	$840	$16,840	$27,288
16	$32,000	4	$4,000	$1,815	$37,815	$53,015
18	$36,000	4	$4,000	$2,055	$42,055	$58,558
7	$14,000	2	$2,000	$840	$16,840	$28,390
15	$30,000	3	$3,000	$1,695	$34,695	$48,470
7	$14,000	2	$2,000	$795	$16,795	$28,758
16	$32,000	4	$4,000	$1,740	$37,740	$52,133
200	$400,000	48	$48,000	$22,605	$470,605	**$683,373**

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT budget
Date: Thursday, December 18, 2003 11:24:51 AM

Dah!

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, December 18, 2003 11:24 AM
To: 'Petrie, Carolyn'
Subject: RE: COT budget

Fine
Sed it when you have it. Also PPB meeting at 12 noon today. I brought in some lemon cake
Rose

-----Original Message-----
From: Petrie, Carolyn [mailto:petrie@rti.org]
Sent: Thursday, December 18, 2003 11:22 AM
To: Higgins, Rosemary (NIH/NICHD)
Subject: COT budget

Rose-

I will change est. # of GDB babies to 25%. If we expect about 40% GDB to be eligible, and from Preemie, expect to enroll about 60%, therefore 25% of GDB babies will enter the study. This will actually spread over three years.

Carolyn Petrie

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

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT Trial
Date: Thursday, October 02, 2003 3:46:50 PM

Rose-

How long should I give the sites to return with comments on the COT trial?

Carolyn

From:	Petrie, Carolyn
To:	"ian.gross@yale.edu"; Poole, W. Kenneth; 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); 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)
Cc:	Higgins, Rosemary (NIH/NICHD); Hastings, Betty J.; Petrie, Carolyn
Subject:	Updated COT Trial
Date:	Thursday, October 02, 2003 3:58:29 PM
Attachments:	COT Schema Oct 1 03.ppt COT study Oct 1 03.doc

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

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	Control
Must Extubate if meets all	**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	Control
May Intubate if EITHER	Must intubate for EITHER if persists > 4hours
PaCO2 > 65 torr	PaCO2 > 55 torr
FiO2 ≥ 50% for SpO2 ≤90%	FiO2 ≥ .50 for SpO2 ≤ 90% (On or off CPAP)

Please note that the FiO2 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 ($\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

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 ≥ 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, <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 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 $\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)
- 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 $\geq$ 90% with an FiO2 $\leq$ 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 $\geq$ 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 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 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).

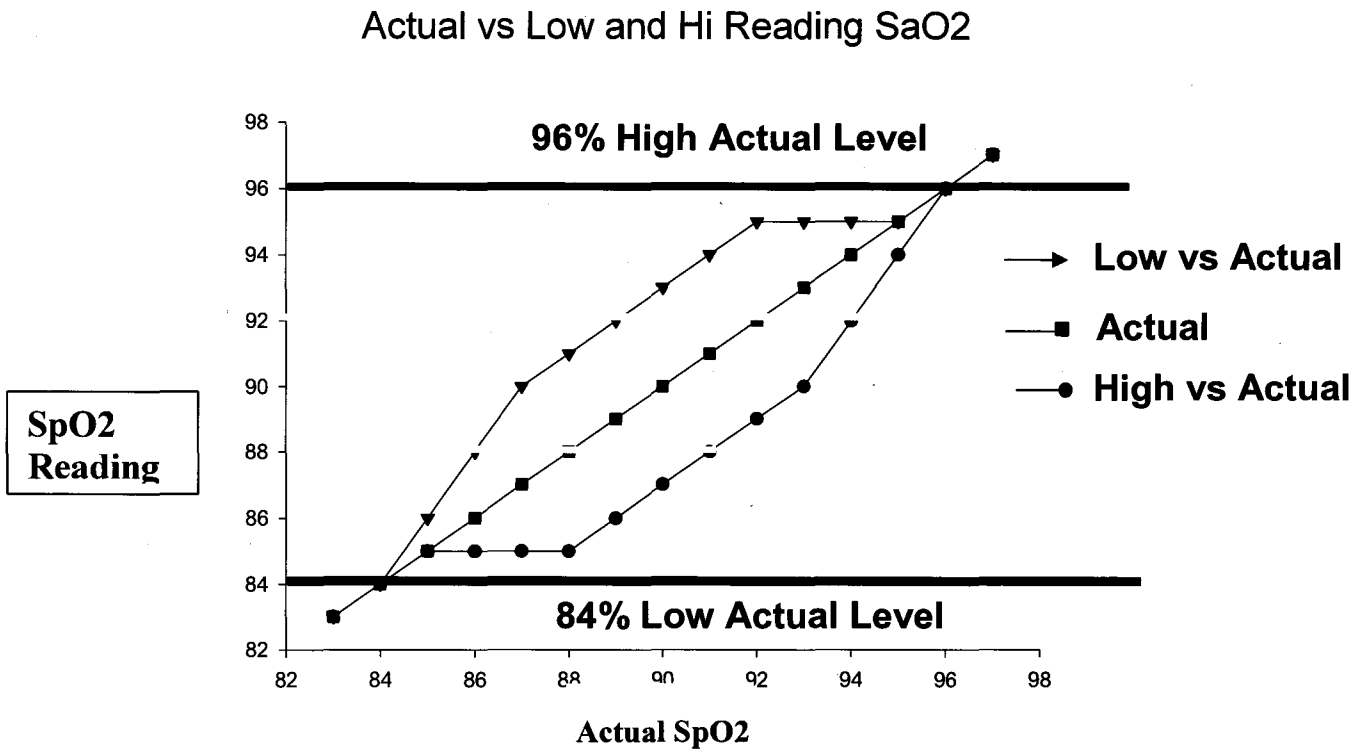
Table. Output and Actual SpO2 Targets and Alarms

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 $\geq$ 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:	Neil Finer
To:	Abbot Laptook
Cc:	Hastings, Betty J.; Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan; William Oh; sshankar@med.wayne.edu; "Ronald GOldberg "; Richard Ehrenkranz; moshea@wfubmc.edu; Jon.E.Tyson@uth.tmc.edu; jlemons@iupui.edu; dstevenson@stanford.edu; dale_phelps@urmc.rochester.edu; barbara_stoll@oz.ped.emory.edu; jobea0@chmcc.org; ian.gross@yale.edu
Subject:	Re: Updated COT Trial
Date:	Tuesday, October 07, 2003 2:31:04 PM
Attachments:	COT Schema Oct 1 03.ppt

Hello Abbot
You are correct. Sorry for the confusion. We intended that the Control Infants must meet both criteria to require intubation. They may be intubated for lesser criteria. I have corrected this mistake.
Many thanks
Neil
----- Original Message -----
From: "Abbot Laptook" <Abbot.Laptook@UTSouthwestern.edu>
To: <nfiner@ucsd.edu>
Sent: Tuesday, October 07, 2003 9:10 AM
Subject: Re: Updated COT Trial

> Neil,
> I am going through the changes in the protocol in order to send out
> to the division. On your 4 slide power point presentation, for
> re-intubation of the control infants you have must intubate for either
> criteria persisting for >4 hrs. However the protocol on both page 15 and
> 16 states that infants must meet both criteria. I assume that the
> protocol is correct and the power point presentation is in error. Is
> this correct? Tx, AL
>
> >>> "Neil Finer" <nfiner@ucsd.edu> 10/2/03 3:17:33 PM >>>
> Hello Everyone
> I noted an important omission in the protocol that was circulated. We
> have allowed 30 + 15 minutes for prophylactic/early surfactant in the
> infants of the 24 and 25 weeks and the protocol states this for the
> Treatment infants. For the Controls this was not clearly stated and
> should read:
> Control Group - Delivery Room Management : 24 - 25 weeks Stratum
> Infants will be intubated in the delivery room and given surfactant or
> receive surfactant within 30 +15 minutes of birth.
>
> In addition the protocol will use the gestational age ranges as 24 and
> 0 /7weeks to 25 and 6/7 and 26 and 0/7 weeks to 27 and 6/7ths. I will
> correct this on subsequent versions
>
> Sorry for any inconvenience. We look forward to your comments.
>
> Neil Finer
>
> ----- Original Message -----
> From: Petrie, Carolyn
> To: 'ian.gross@yale.edu' ; Poole, W. Kenneth ; 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)
> ; 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)
> Cc: aRose Higgins (higginsr@mail.nih.gov) ; Hastings, Betty J. ;
> Petrie, Carolyn
> Sent: Thursday, October 02, 2003 12:54 PM
> Subject: Updated COT Trial
>
>
>
> 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
>
>

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

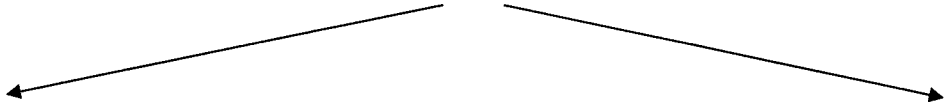
Treatment	Control
Delivery Room	
DR CPAP/PEEP Intubate only for Resus	MAY receive Prophylactic Surf
NICU	
Intubation Criteria May Intubate if meets ANY one of criteria	Control Infants not intubated in DR MUST be intubated for surfactant If meets ANY one of criteria < 72 hrs
FiO2 >.50 for SpO2 ≤ 90% PaCO2 > 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

PaCO2 > 65 torr

FiO2 ≥ 50% for SpO2 ≤90%

Control

Must intubate for BOTH
if persist > 4hours

PaCO2 > 55 torr

FiO2 ≥ .50 for SpO2 ≤ 90%
(On or off CPAP)

Please note that the FiO2 criteria are similar.
Control infants MUST be intubated if they meet Both of these Criteria whereas Treatment infants MAY be intubated if they meet Criteria
Control Infants may be re-intubated at lesser criteria
These Criteria will be in effect for the first 28 days of life

From: Hastings, Betty J.
To: "Barbara Stoll"
Cc: M. D. Neil Finer (nfiner@ucsd.edu); Higgins, Rosemary (NIH/NICHD); Petrie, Carolyn
Subject: RE: Updated COT Trial
Date: Thursday, October 09, 2003 8:32:23 AM

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: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: cot
Date: Thursday, October 09, 2003 10:01:51 AM

Do we need a COT conf call?

Carolyn Petrie

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

From:	Petrie, Carolyn
To:	Higgins, Rosemary (NIH/NICHD)
Subject:	FW: Updated COT Trial
Date:	Thursday, October 09, 2003 11:14:42 AM
Attachments:	COT Schema Oct 1 03.ppt COT study Oct 1 03.doc

-----Original Message-----
From: Petrie, Carolyn
Sent: Thursday, October 02, 2003 3:54 PM
To: 'ian.gross@yale.edu'; Poole, W. Kenneth; 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); 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)
Cc: aRose Higgins (higginsr@mail.nih.gov); Hastings, Betty J.; Petrie, Carolyn
Subject: Updated COT Trial

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:	Barbara Stoll
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:	Thursday, October 09, 2003 12:38:13 PM

Hi Barbara

We are not making any further changes till we hear from the sites. Please consider the current protocol and the revised PowerPoint as the definitive protocol. I am sure that as we move ahead there will be some further minor changes. The current version reflects the input of the Steering Committee meeting and all the responses that we received. We have discussed that we should do the following:

Develop 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.

Have one of the research nurses at each site 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.

These will be developed as part of the Study Manual, once we have agreed and approved the Protocol.

Regards

Neil

---- Original Message -----
From: "Barbara Stoll" <barbara.stoll@oz.ped.emory.edu>
To: "Neil Finer" <nfiner@ucsd.edu>
Cc: "Hastings, Betty J." <bkh@rti.org>; <higginsr@mail.nih.gov>
Sent: Wednesday, October 08, 2003 2:30 PM
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:	Hastings, Betty J.; "Barbara Stoll"
Cc:	Higgins, Rosemary (NIH/NICHD); Petrie, Carolyn
Subject:	Re: Updated COT Trial
Date:	Thursday, October 09, 2003 2:31:14 PM
Attachments:	COT Summary.doc

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
>

COT Study: A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants

Summary of Trial

Study Design

This will be a prospective, randomized, factorial 2X2 design multi-center trial.. 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 ($\leq$ 60 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.

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.

Study Intervention: Ventilation

There are 2 strata, infants of 24 0/7ths to 25 6/7ths weeks and infants of 26 0/7ths to 27 6/7ths weeks. All Treatment and Control infants of 24 0/7ths to 25 6/7ths weeks will receive prophylactic surfactant, and the Treatment infants who meet criteria will be extubated at 1 hour and be placed on CPAP.

In the 26 0/7ths to 27 6/7ths 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 criteria for intubation and extubation for the Treatment Group infants will require higher FiO2 and higher PaCO2, and higher ventilator settings than those used for the Control Group. Treatment infants MUST be extubated when they meet criteria, whereas Control infants MAY be extubated when the meet criteria, but can continue intubated at the discretion of the Neonatologist. The intent is to force Treatment infants to extubation and to management with CPAP.

Study Intervention: Low versus High SpO2 Range:

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.

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) will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above.

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 %

Overall Design

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

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: Updated COT Trial
Date:	Thursday, October 09, 2003 2:31:40 PM
Attachments:	COT Summary.doc

----- 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:	"Cynthia Cole, MD"
Cc:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	POST-ROP
Date:	Thursday, October 16, 2003 4:32:23 PM
Attachments:	SpO2 Intervention COT and Post ROP Sept 30.doc

Hi Cynthia
I had sent out this e-mail Sept 30th and got a response form Bill Hay. I have forwarded you a copy today and have also attached the same document here. I had thought that everyone received it. I am resending the message and attachments to you, and will let you send it to your group, with your comments. As you will see, I had indicated the ranges for the COT trial that are exactly what we discussed this morning. I have attached the excerpts from the protocol for your review. If there is agreement, I would like to let Masimo know as they will need to begin testing at their end to ensure appropriate function. I look forward to your reply. I will let you know as soon as the COT trial receives official approval.
Regards
NeilConfidentiality Notice:

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).

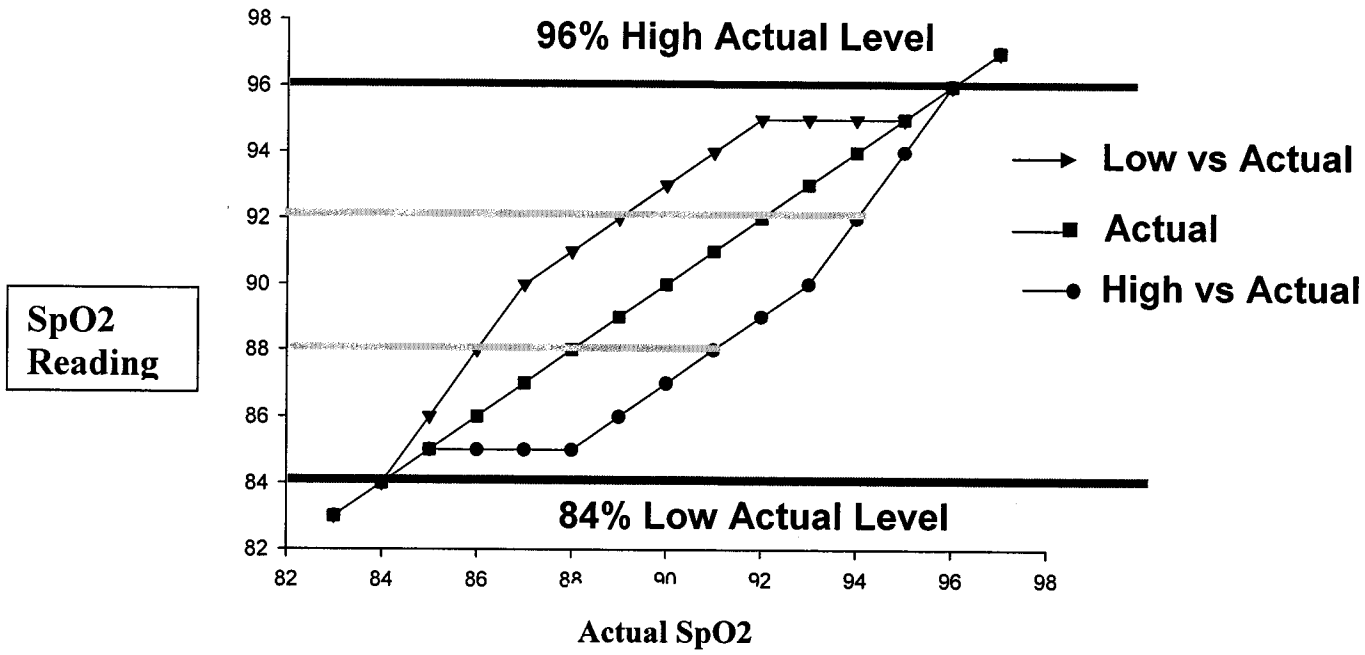
Table. Output and Actual SpO2 Targets and Alarms

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.

Actual vs Low and Hi Reading SaO2



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:	Neil Finer
To:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	COT Trial
Date:	Wednesday, October 22, 2003 7:23:48 PM

Hi
I will call you all at 3:00 PM Eastern time tomorrow.
Talk to you then.
Neil

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:	COT Trial
Date:	Thursday, October 30, 2003 12:04:44 AM
Attachments:	COT study Oct 29 03.doc

Hi Rose
Lets run with this version. Our group has made some changes which should make this study even more acceptable to the Network.
Please circulate to the outside reviewers.
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

Oct 29, 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]

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 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.

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 $\geq$ 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 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 0/7ths to 25 6/7ths weeks will receive prophylactic surfactant. In the 26 0/7ths to 27 6/7ths 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.

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. The delivery room management for both Treatment and Control infants in this strata will be identical, and thus these infants will receive prophylactic surfactant.

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 intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth. They will be weighed on admission to the NICU.

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 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 MAY 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)
- 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.

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 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 $\pm$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.

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 > .40 with or without CPAP with an SpO2 < 90% 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 $\geq$ 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 > .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.

<u>For all Infants, Both Strata</u>

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.

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.

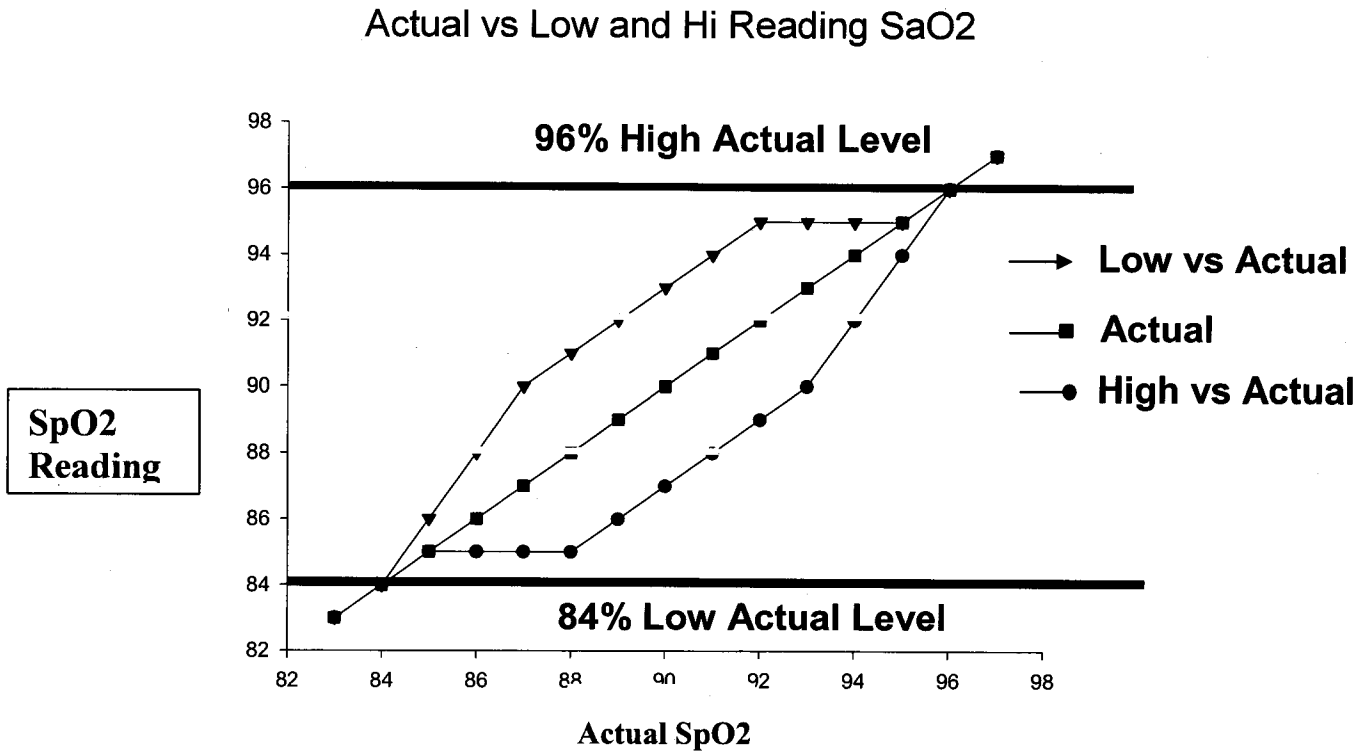
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.


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

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 $\geq$ 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: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT TRIAL
Date: Thursday, October 30, 2003 12:16:05 PM

I will give them three weeks as well. Let me know otherwise.

Carolyn

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 30, 2003 12:07 PM
To: 'petrie@rti.org'
Subject: COT TRIAL

Carolyn
Can you send this protocol to the advisory board and the DSMC?
Thanks
Rose

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

301-496-3790 (FAX)

From:	Petrie, Carolyn
To:	George Rhoads MD (rhoads@rwja.umdnj.edu); John Sinclair MD (sinclair@mcmaster.ca); Larry Gilstrap MD (Larry.C.Gilstrap@uth.tmc.edu); M. D. Alan Jobe (Jobea0@chmcc.org); Mark Klebanoff MD (mk90h@nih.gov); Roberta Ballard MD (ballard@email.chop.edu); Carol Redmond Ph. D. (ckr3+@pitt.edu); John C. Fletcher Ph. D. (jcf4x@unix.mail.virginia.edu); M. D. Christine A. Gleason (cgleason@u.washington.edu); M. D. Gordon Avery (gavery@cnmc.org); M. D. Mary D"Alton (md511@columbia.edu)
Cc:	Hastings, Betty J.; Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth
Subject:	Neonatal Research Network COT TRIAL
Date:	Friday, October 31, 2003 3:23:11 PM
Attachments:	COT Study October 31 2003.doc

Good Afternoon!

The attached study, "Continuous Positive Airway Pressure and Oxygenation Trial (COT Study): A Factorial Randomized Control Trial in Extremely Low Birth Weight Infants" was approved by the Neonatal Research Network.

Please review and send me your comments by **Friday November 21**.

Thank you,
Carolyn Petrie

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

Protocol for the NICHD Neonatal Research Network

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

October 29, 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 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

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 relative to infants managed with a higher SpO2 range (91% to 95%) 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.

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 $\geq$ 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 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 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

Within site and within gestational age strata, randomization will occur prior to delivery and will be performed by utilizing specially prepared double-sealed envelopes. Each randomization will indicate either CPAP and permissive ventilation management or conventional management with early surfactant 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 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 0/7ths to 25 6/7ths weeks will receive prophylactic surfactant. In the 26 0/7ths to 27 6/7ths 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.

For infants in the 24 0/7ths to 25 6/7ths weeks gestation stratum, 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. The delivery room management for both Treatment and Control infants in this strata will be identical, and thus these infants will receive prophylactic surfactant.

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 intubated in the delivery room and given surfactant within 30 ± 15 minutes of birth. They will be weighed on admission to the NICU.

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 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 MAY 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)
- 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.

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 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. 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.

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 > .40 with or without CPAP with an SpO2 < 90% 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 $\geq$ 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 > .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 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).

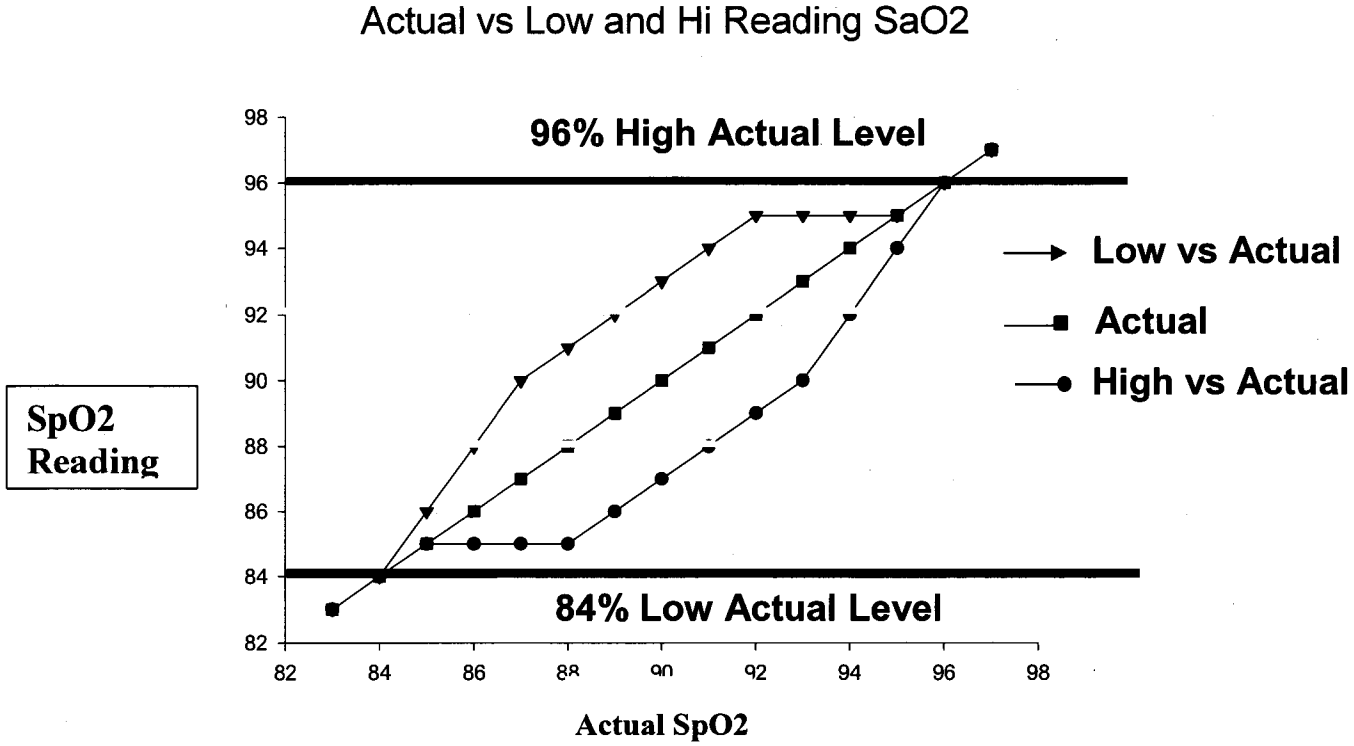
Table. Output and Actual SpO2 Targets and Alarms

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.[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 outcomes 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.

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% and 90% power. These represent the total numbers enrolled. To correct for two outcomes, we chose a conservative 2% level of significance 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 1000 infants for the acute outcomes. Adjusting for attrition until follow-up, this means that a total of 1170 infants would have to be enrolled to 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 continuous 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:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject:	COT Trial
Date:	Tuesday, September 09, 2003 8:44:18 PM
Attachments:	COT study Sept 9 03.doc COT Trial Sept 17.ppt

Hello Everyone

I have developed a PowerPoint presentation with the help of Bill Oh - he made one for his group and I use some of his slides.

I have also made some changes to the protocol to reflect many of the comments that I received. I would like to circulate these or at least the PowerPoint to the sites for their review tomorrow.

Please let me have your thoughts.

Be well

Neil

Protocol for the NICHD Neonatal Research Network

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

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 ($\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.[293031] 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 ($\leq$ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control	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.[27,464748] 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 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
- 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,
- 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 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)
- 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 adminsiutration 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
- 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)

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.

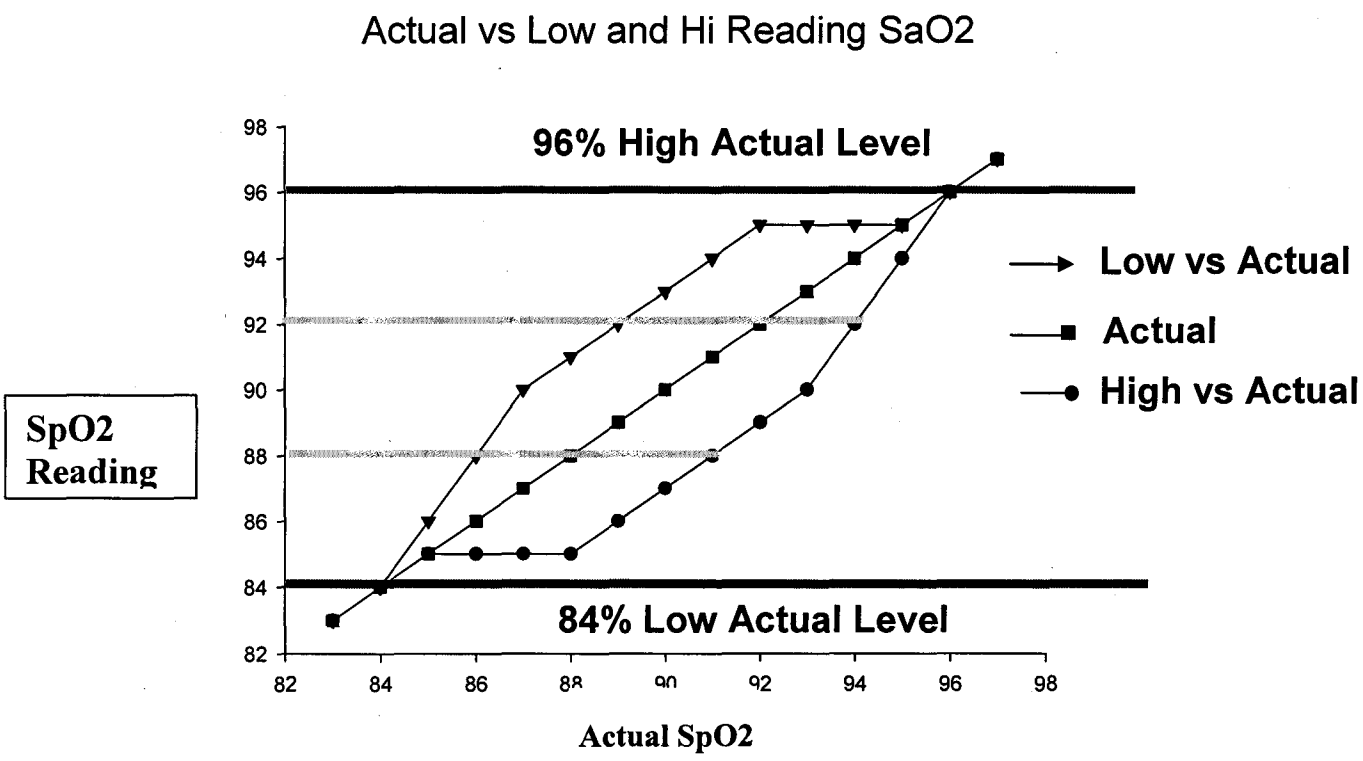
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.[49][50][51]. 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.[52]

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)[53]
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 .

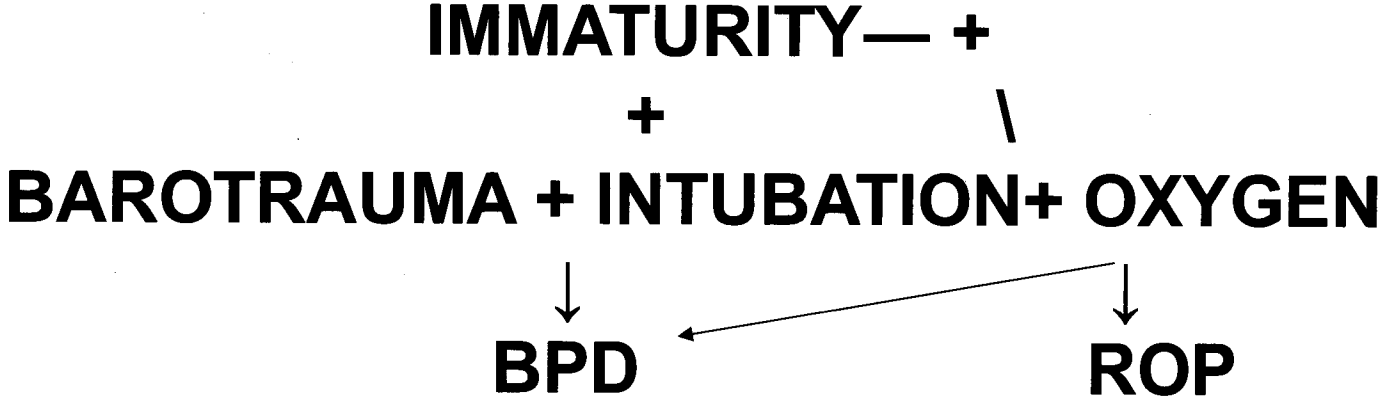
51 Khalaf, M. N.; Brodsky, N.; Hurley, J., and Bhandari, V A prospective randomized, controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001; 108(1):13-17

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

53 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

BACKGROUND

PATHOGENESIS



BACKGROUND-CONT'D

- ANIMAL DATA SHOWED THAT EARLY SHORT VENTILATION (REF 8), AND PEEP IMPROVES FRC AND REDUCES LUNG INJURY(REF. 9,10)

- CORROBORATED BY RETROPESPECTIVE CLINICAL EXPERIENCE
- Lacking PROSPECTIVE TRIALS

NETWORK FEASIBILITY STUDY

- CONDUCTED IN 5 SITES
- OBJECTIVE : TEST FEASIBILITY OF THE STUDY DESIGN
- N=104; 55 CPAP; 49 CONTROL
- CRITERIA FOR FEASIBILITY: >90% OF RANDOMIZED INFANTS FOLLOWED THE PRESCRIBED PROTOCOL
- RESULTED IN REMOVAL OF INFANTS OF < 24 WEEKS BECAUSE OF UNIVERSAL NEED FOR DELIVERY ROOM INTUBATION FOR RESUSCITATION

COT Trial

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

COT Trial

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

PRIMARY HYPOTHESIS

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

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

COT Trial: Inclusion Criteria

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

COT Trial: Exclusion Criteria

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

COT Trial - Ventilation Arm

- Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic surfactant in the delivery area for all but those who require minimal oxygen
- Will force early surfactant use (by 1 hour) in untreated infants who meet criteria

COT Trial Ventilation Arm

- Treatment infants will be forced to early extubation attempt at higher ventilation settings
- Control infants will be extubated at more conventional settings
- Spontaneous extubation will not require mandatory re-intubation, unless intubation criteria are met.

Intubation Criteria

Treatment Group
May be intubated

- An FiO2 >0.5 to maintain an indicated SpO2 $\geq$ 90%
- pH < 7.20-7.25 and/or PaCO2 > 65 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock or surgery

Control Group
Must be intubated

- An FiO2 >0.4 to maintain an indicated SpO2 $\geq$ 90%
- The use of CPAP and an FiO2 > .30
- pH < 7.25 and/or PaCO2 > 50 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or surgery

Extubation Criteria – For first 28 days

Treatment Group

Must be Extubated

- PaCO2 < 65 torr with a pH > 7.20 - 7.25
- An SpO2 $\geq$ 90% with an FiO2 $\leq$ 50%
- (MAP) < 10 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

Control Group

May be Extubated

- PaCO2 < 50 torr and/or pH > 7.25
- An SpO2 > 90% with an FiO2 < .40
- MAP < 8 cm H2O, ventilator rate < 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)

Oxygen Saturation Monitoring Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter

SpO2 Targets

SpO2 – 85% - 89% | **SpO2 – 91% - 95%**

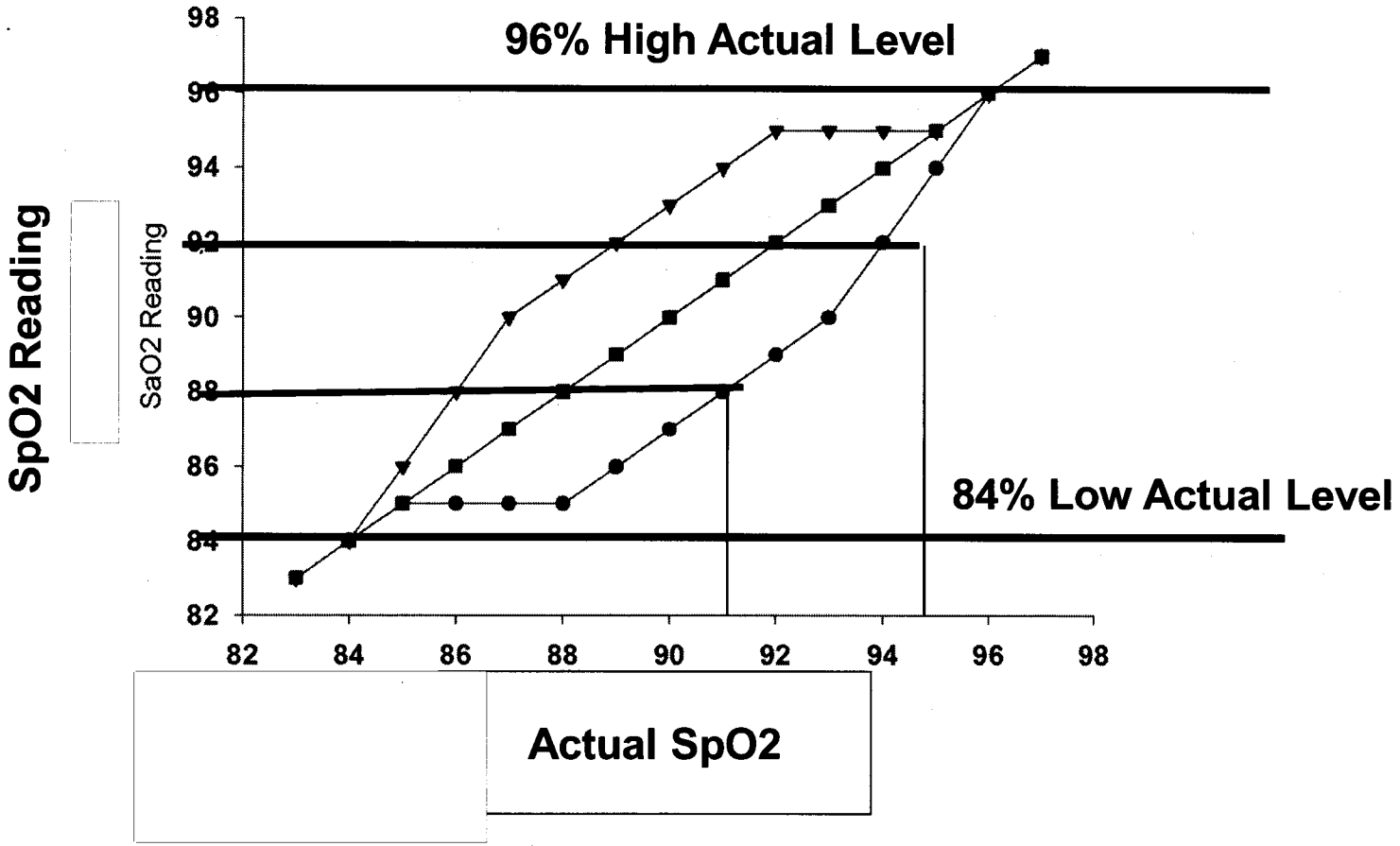
Maintain till off ventilatory support and Oxygen

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

OXYGENATION PROTOCOL

- LOW RANGE: TARGET SpO2 85-89%
- HIGH RANGE: TARGET SpO2 90-95%
- STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE
- STUDY PO'S READING NOT THE ACTUAL SpO2 for READINGS BETWEEN 85% TO 95% FOR BLINDING
- OUTPUT TARGET AND ALARM FOR BOTH GROUPS WILL BE SET AT 88-92% AND 85-95% RESPECTIVELY
- SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED

Plot of Actual versus Displayed SpO2



OXYGENATION PROTOCOL-CONT'D

- **STUDY PO WILL REMAIN WITH INFANT UNTIL:**
  - **OFF VENTILATOR OR**
  - **OFF OXYGEN**
  - **ACTUAL SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER WEEK DURING STUDY**

Sample Size Estimate

- The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Occurrence of Death (D) and BPD, CLD and NDI for each Possible Study Subgroup

Subgroup	D/BPD	D/> Stage III ROP	D/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

Sample Size

- We will use a 10% difference and a power of 80% for the outcomes of Death/BPD and Death/ROP
- This will require a sample size of 1170 infants
- Adding 15% attrition factor results in a total of 1345 infants.
- This will also provide an 80% power to evaluate Mortality/NDI.

PROPOSED MODIFICATIONS

- If a Control infant accidentally extubates, they may be left extubated
- Caffeine will be utilized for all at least 1 hour prior to planned extubation, or at first occurrence of clinically significant apnea.
- Surfactant redosing would follow manufacturer's guidelines for timing ie q 6 – 12 hours for up to 4 doses
- Indications for repeat surfactant:

FiO2 > .50 in Treatment and > .40 in Controls

PROPOSED MODIFICATIONS

- For treated infants, extubation ma be attempted *within 24 hours* of meeting criteria
- If Treatment infant required re-intubation, can wait for 24-48 hours before further attempt at extubation

Other Considerations

- Control Infants will potentially benefit because they will receive prophylactic surfactant – Only those not requiring CPAP and/or Oxygen > 30% by 60 minutes will avoid early surfactant
- This is not current Network practice with only 5 of 16 centers giving surfactant to more than 95% of their infants of 26 to 27 weeks
- Overall, 82% of NICHD infants in this group receive surfactant, but we are uncertain of the actual timing.

QUESTIONS FOR THE GROUP

- IS THE STUDY FEASIBLE IN OUR SITE
- SUGGESTIONS THAT WILL IMPROVE FEASIBILITY
- IMPORTANCE OF THIS STUDY
- IS THERE ETHICAL CONCERN
- ANTICIPATED STUDY DIFFICULTY-IS EQUIPOIS A PROBLEM

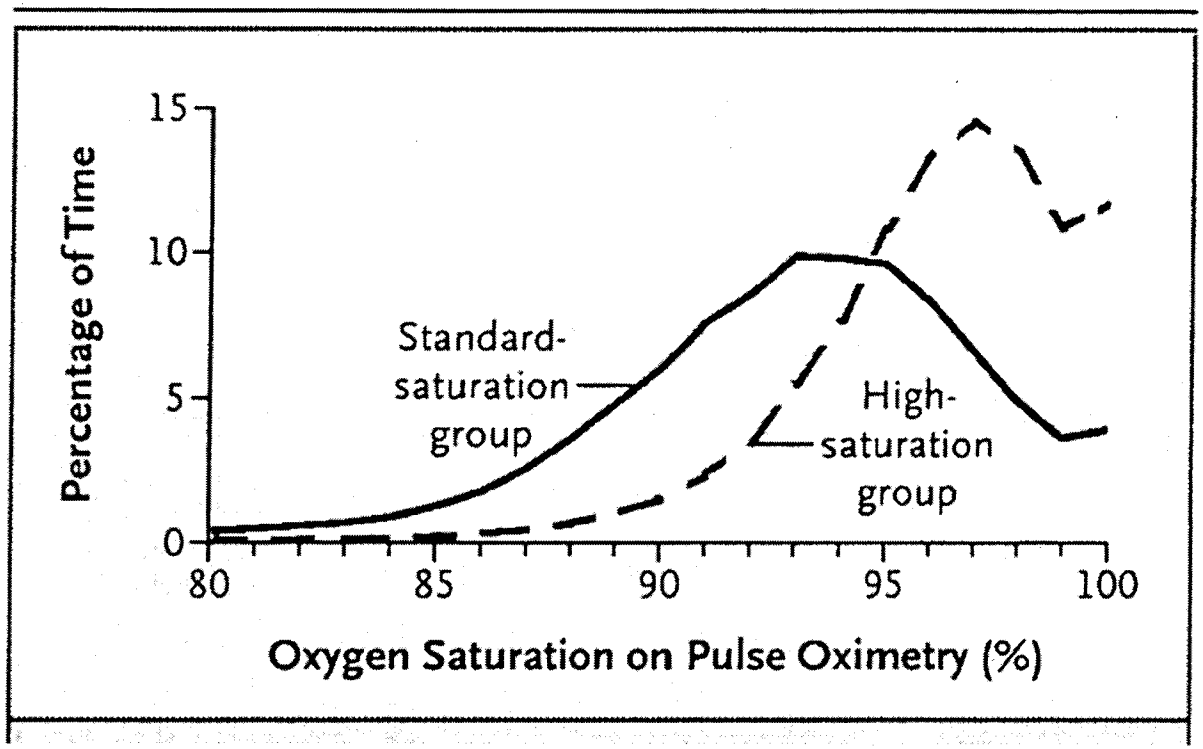
OTHER CONSIDERATIONS

- No other trial has prospectively evaluated the SpO2 level from birth onwards
- BOOST and STOP-ROP began when infants were $\geq$ 32 weeks of age
- They used ranges of 91-94% and 95-98%
- They both reported more pulmonary morbidity and a longer need for oxygen in their high saturation group where SpO2 was $\geq$ 95%
- Our study will keep SpO2 $\leq$ 95% for both groups

BOOST Trial
Askie et al, NEJM 2003;349;959

- BOOST used a 2% adjustment in the SpO2 reading
- Low range infants read 2% lower than actual and hi range infants read 2% higher throughout the entire SpO2 range.
- Target range was 93 – 96%

SpO2 from BOOST Trial
Askie et al NEJM 2003;349:959-67



QUESTIONS FOR THE GROUP

- IS THE STUDY FEASIBLE IN OUR SITE
- SUGGESTIONS THAT WILL IMPROVE FEASIBILITY
- IMPORTANCE OF THIS STUDY
- IS THERE ETHICAL CONCERN
- ANTICIPATED STUDY DIFFICULTY-IS EQUIPOIS A PROBLEM

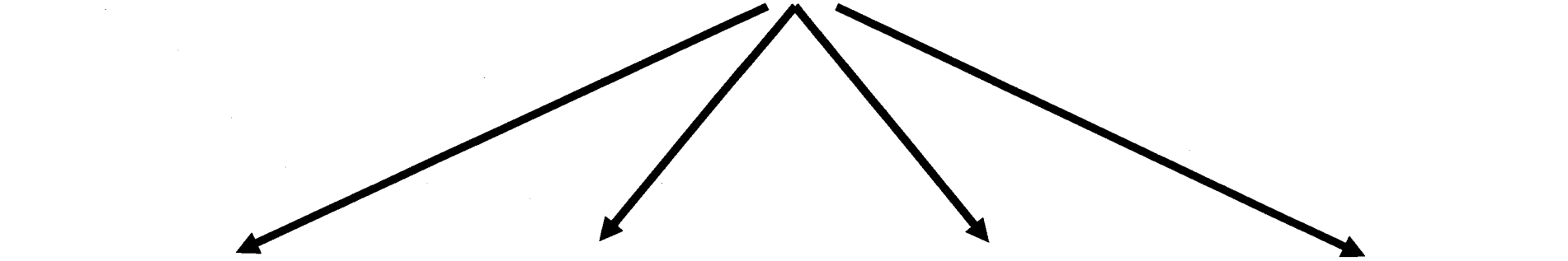
QUESTIONS FOR THE GROUP

- IS THE STUDY FEASIBLE IN OUR SITE
- SUGGESTIONS THAT WILL IMPROVE FEASIBILITY
- IMPORTANCE OF THIS STUDY
- IS THERE ETHICAL CONCERN
- ANTICIPATED STUDY DIFFICULTY-IS EQUIPOIS A PROBLEM

QUESTIONS FOR THE GROUP

- IS THE STUDY FEASIBLE IN OUR SITE
- SUGGESTIONS THAT WILL IMPROVE FEASIBILITY
- IMPORTANCE OF THIS STUDY
- IS THERE ETHICAL CONCERN
- ANTICIPATED STUDY DIFFICULTY-IS EQUIPOIS A PROBLEM

Overall Study Design



CPAP = Treatment Group

SOC = Control Group

COT Trial

Ventilation Strategy

Strata= 24-25 & 26-276/7th wks

CPAP Both Strata

CPAP in DR

Intubated in DR for Resus Only
Or if meet criteria at 60 minutes
Receive Surf when intubated
Fi02 > 50% for Sp02 ≥ 90% > 15 min

Control

All 24-25 wks
intubated in DR
< 15 min for Surf

26-27 wks
May intubate for
Surf < 15 min
Or when meet criteria

Later CRITERIA for INTUBATION

FiO2 >0.5 to maintain SpO2 ≥ 90%
pH < 7.20-7.25 and/or PaCO2 > 65 torr

FiO2 >0.4 with SpO2 ≥ 90%
The use of CPAP and an FiO2 > .30
pH < 7.25 and/or PaCO2 > 50 torr

Apnea requiring bag and mask ventilation
The occurrence of sepsis, shock, or surgery

Suggestions

- Additional nursing time may be required and budgeted to assess whether the protocol is being followed perhaps BID.

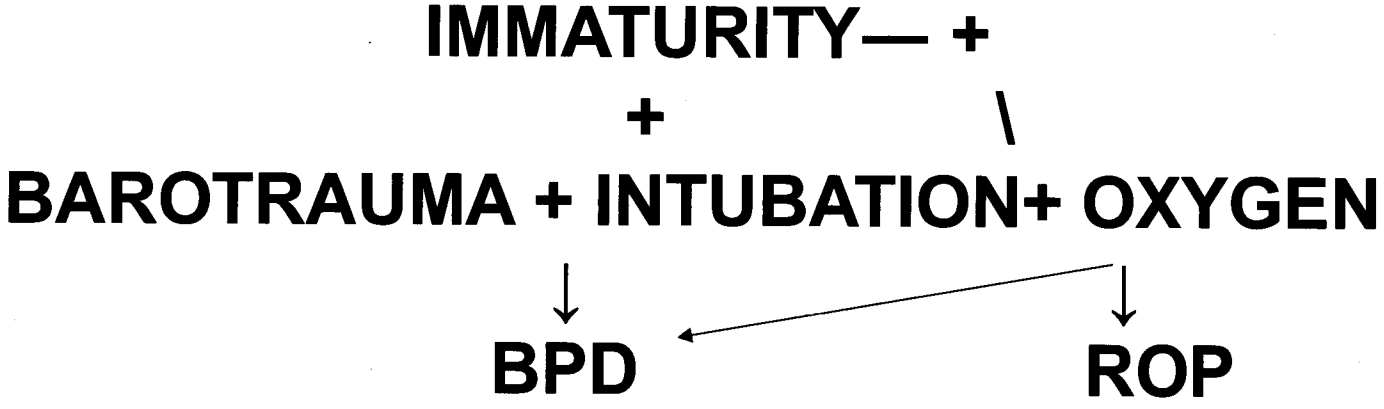
From:	Neil Finer
To:	Petrie, Carolyn; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth; abbot.laptook@utsouthwestern.edu; Jobea0@chmcc.org; aaf2@po.cwru.edu; barbara_stoll@oz.ped.emory.edu; dale_phelps@urmc.rochester.edu; dstevenson@stanford.edu; edward.donovan@chmcc.org; jlemons@iupui.edu; jon.e.tyson@uth.tmc.edu; 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; Carl_Dangio@urmc.rochester.edu; BENJA005@onyx.dcri.duke.edu; vanmeurs@leland.stanford.edu; martin.l.blakely@uth.tmc.edu; mcw3@po.cwru.edu; Brenda.H.Morris@uth.tmc.edu; bvohr@wihri.org; cotte010@mc.duke.edu; Hastings, Betty J.; McClure, Beth; Das, Abhik; Pagliaro, Susan (NIH/NICHD)
Cc:	Petrie, Carolyn
Subject:	Re:COT Trial
Date:	Wednesday, September 10, 2003 7:17:12 PM
Attachments:	COT Trial Sept Steering Comm.ppt COT study Sept 9 03.doc

---

Hello Everyone
I am attaching a PowerPoint presentation of the COT trial for discussion at your site and at the Steering Committee. I have made changes reflecting the input that I received from a number of you, and I appreciate all your input. I am also attaching a draft of the protocol with changes noted in yellow highlight.
I hope that we can have a good discussion at the meeting.
Regards
Neil Finer

BACKGROUND

PATHOGENESIS



BACKGROUND-CONT'D

- ANIMAL DATA SHOWED THAT EARLY SHORT VENTILATION (REF 8), AND PEEP IMPROVES FRC AND REDUCES LUNG INJURY(REF. 9,10)

- CORROBORATED BY RETROPESPECTIVE CLINICAL EXPERIENCE
- Lacking PROSPECTIVE TRIALS

NETWORK FEASIBILITY STUDY

- CONDUCTED IN 5 SITES
- OBJECTIVE : TEST FEASIBILITY OF THE STUDY DESIGN
- N=104; 55 CPAP; 49 CONTROL
- CRITERIA FOR FEASIBILITY: >90% OF RANDOMIZED INFANTS FOLLOWED THE PRESCRIBED PROTOCOL
- RESULTED IN REMOVAL OF INFANTS OF < 24 WEEKS BECAUSE OF UNIVERSAL NEED FOR DELIVERY ROOM INTUBATION FOR RESUSCITATION

COT Trial

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

COT Trial

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

PRIMARY HYPOTHESIS

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

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

COT Trial: Inclusion Criteria

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

COT Trial: Exclusion Criteria

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

COT Trial - Ventilation Arm

- Will test the use of early CPAP started in the delivery area combined with a permissive ventilator strategy compared to a standard of care approach involving prophylactic surfactant in the delivery area for all but those who require minimal oxygen
- Will force early surfactant use (by 1 hour) in untreated infants who meet criteria

COT Trial Ventilation Arm

- Treatment infants will be forced to early extubation attempt at higher ventilation settings
- Control infants will be extubated at more conventional settings
- Spontaneous extubation will not require mandatory re-intubation, unless intubation criteria are met.

Intubation Criteria

Treatment Group
May be intubated*

- CPAP FiO2 >0.5 to maintain an indicated SpO2 ≥ 90%
- pH < 7.20-7.25 and/or PaCO2 > 65 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock or surgery
- * Minimum criteria, may be exceeded by MD choice

Control Group
Must be intubated

- Hood FiO2 >0.4 to maintain an indicated SpO2 ≥ 90%
- CPAP FiO2 >0.3 to maintain SpO2 ≥ 90%
- pH < 7.25 and/or PaCO2 > 50 torr
- Apnea requiring bag and mask ventilation
- The occurrence of sepsis, shock, or surgery

Extubation Criteria – For first 28 days

Treatment Group

Must be Extubated

- PaCO2 < 65 torr with a pH > 7.20 - 7.25
- An SpO2 ≥ 90% with an FiO2 ≤ 50%
- (MAP) < 10 cm H2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)

Control Group

May be Extubated

- PaCO2 < 50 torr and/or pH > 7.25
- An SpO2 > 90% with an FiO2 ≤ .40
- MAP < 8 cm H2O, ventilator rate ≤ 15 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)

Oxygen Saturation Monitoring Strategy

Birth – Admit to NICU
Placed on Study Pulse Oximeter

SpO2 Targets

SpO2 – 85% - 89%

SpO2 – 91% - 95%

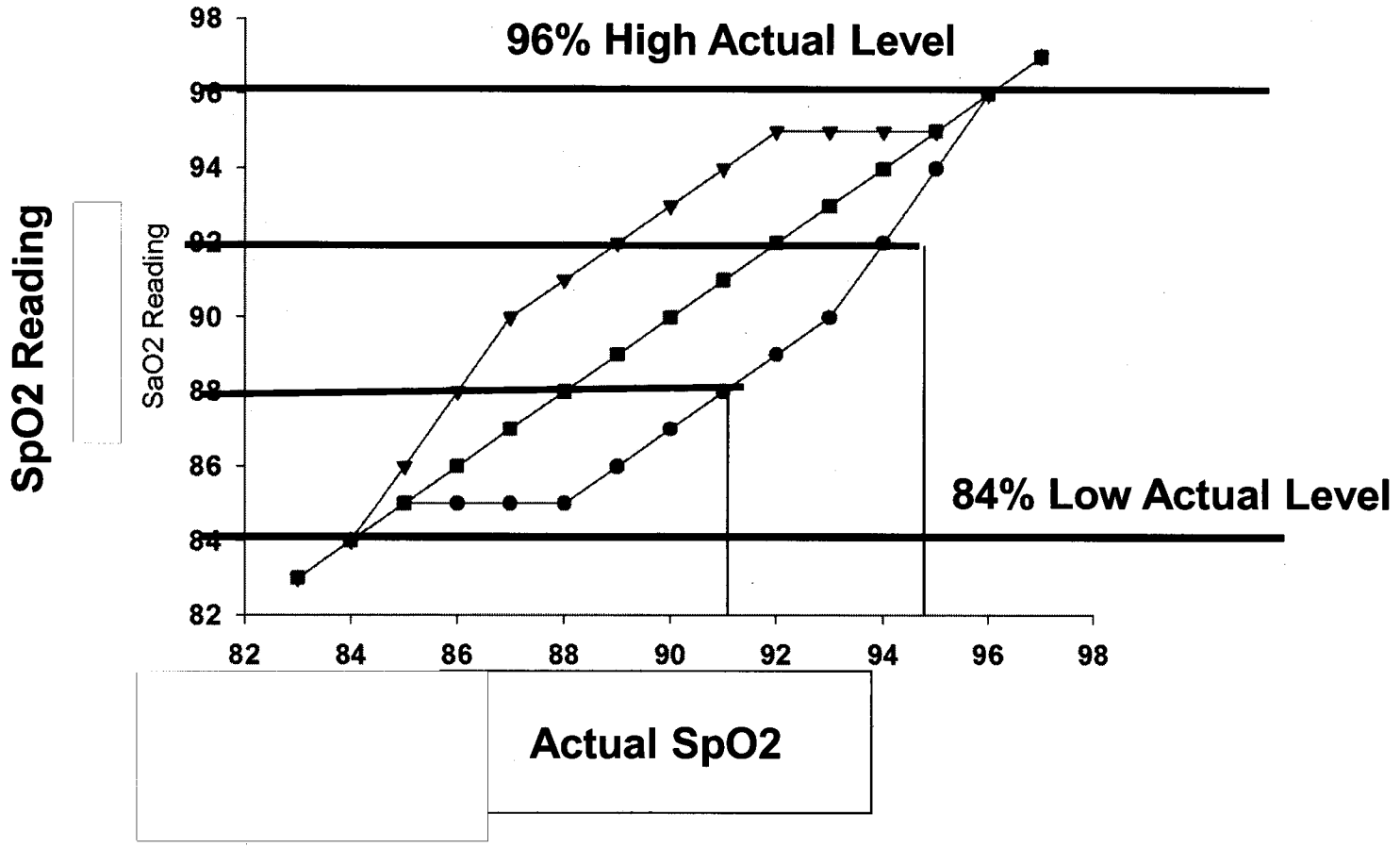
Maintain till off ventilatory support and Oxygen

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

OXYGENATION PROTOCOL

- LOW RANGE: TARGET SpO2 85-89%
- HIGH RANGE: TARGET SpO2 91-95%
- STUDY PULSE OXIMETERS (PO) WILL BE SUPPLIED TO PARTICIPATING SITE
- STUDY PO'S READING NOT THE ACTUAL SpO2 for READINGS BETWEEN 85% TO 95% FOR BLINDING
- OUTPUT TARGET AND ALARM FOR BOTH GROUPS WILL BE SET AT 88-92% AND 85-95% RESPECTIVELY
- SPO2 READINGS BELOW 85% AND ABOVE 95% WILL BE ACTUAL, NOT ALTERED

Plot of Actual versus Displayed SpO2



OXYGENATION PROTOCOL-CONT'D

- STUDY PO WILL REMAIN WITH INFANT UNTIL:
  - OFF VENTILATOR OR
  - OFF OXYGEN
  - ACTUAL SpO2 FROM STUDY PO WILL BE DOWNLOADED TO RTI ONCE PER WEEK DURING STUDY

Sample Size Estimate

- The sample size depends on the outcome rate only through the standard deviation of the rate and this turns out to be essentially 50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

Occurrence of Death (D) and BPD, ROP and NDI for each Possible Study Subgroup

Subgroup	D/BPD	D/> Stage III ROP	D/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

Sample Size

- We will use a 10% difference and a power of 80% for the outcomes of Death/BPD and Death/ROP
- This will require a sample size of 1170 infants
- Adding 15% attrition factor results in a total of 1345 infants.
- This will also provide an 80% power to evaluate Mortality/NDI.

PROPOSED MODIFICATIONS

- If a Control infant accidentally extubates, they may be left extubated
- Caffeine will be utilized for all at least 1 hour prior to planned extubation, or at first occurrence of clinically significant apnea.
- Surfactant redosing would follow manufacturer's guidelines for timing ie q 6 – 12 hours for up to 4 doses
- Indications for repeat surfactant:

FiO2 > .50 in Treatment and > .40 in Controls

PROPOSED MODIFICATIONS

- For treated infants, extubation may be attempted *within 24 hours* of meeting criteria
- If Treatment infant required re-intubation, can wait for 24 - 48 hours before further attempt at extubation

Other Considerations

- Control Infants will potentially benefit because they will receive prophylactic surfactant – Only those not requiring CPAP and Oxygen > 30% by 60 minutes will avoid early surfactant
- Prophylactic surfactant in this GA is not current Network practice, with only 5 of 16 centers giving surfactant to more than 95% of their infants of 26 to 27 weeks
- Overall, 82% of NICHD infants of this GA receive surfactant (GDB), but we are uncertain of timing.

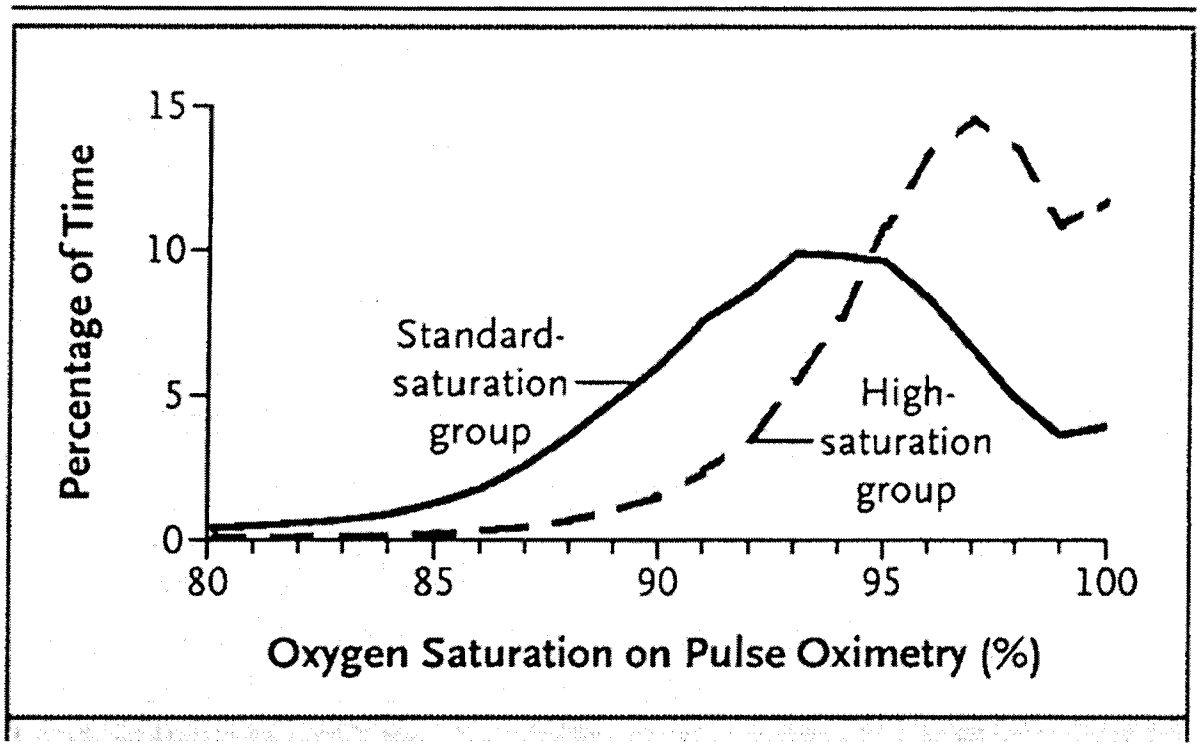
OTHER CONSIDERATIONS

- No other trial has prospectively evaluated the SpO2 level from birth onwards
- BOOST and STOP-ROP began when infants were $\geq$ 32 weeks of age
- They used ranges of 91-94% and 95-98%
- They both reported more pulmonary morbidity and a longer need for oxygen in their high saturation group where SpO2 was $\geq$ 95%
- Our study will keep SpO2 $\leq$ 95% for both groups

BOOST Trial
Askie et al, NEJM 2003;349;959

- BOOST used a 2% adjustment in the SpO2 reading
- Low range infants read 2% lower than actual and hi range infants read 2% higher throughout the entire SpO2 range.
- Target range was 93 – 96%

SpO2 from BOOST Trial
Askie et al NEJM 2003;349:959-67



QUESTIONS FOR THE GROUP

- IS THE STUDY FEASIBLE IN OUR SITE
- SUGGESTIONS THAT WILL IMPROVE FEASIBILITY
- IMPORTANCE OF THIS STUDY
- ARE THERE ETHICAL CONCERNS
- ANTICIPATED STUDY DIFFICULTY-IS EQUIPOIS A PROBLEM

From: CHMCC Groupwise
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: DR CPAP call
Date: Tuesday, September 16, 2003 9:54:16 AM

You are so organized – how about 3 min. Like the senate – one center can deed its time to another. (no way – need to limit Tyson)

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: COT
Date: Wednesday, September 17, 2003 1:56:13 PM

I agree
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Sent: Wednesday, September 17, 2003 10:37 AM
Subject: COT

Neil
I got a couple of emails requesting than we discuss the major areas of contention on the call. Alan thinks this should be the way we go.
I sent the Steering committee an email.

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)
Cc: mcw3@cwru.edu
Subject: Re: CPAP Trial (COT)
Date: Wednesday, September 17, 2003 4:30:15 PM

> CWRU is enthusuastic about the COT trial and wishes to participate

YES

Av

From:	Edward Donovan
To:	Higgins, Rosemary (NIH/NICHD)
Subject:	CPAP
Date:	Wednesday, September 17, 2003 4:39:28 PM

Rose,
I will enthusiastically work with all of our faculty, fellows, nurses and RTs to make this study a success in Cincinnati.
I think that this is a very important study for the Network because this is "bread and butter" neonatology.
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:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject:	COT
Date:	Wednesday, September 17, 2003 8:49:33 PM
Attachments:	COT-Schema - Steering Comm.ppt COT Revision Post Steering Comm Sept 17.doc

Hello Everyone
I have redesigned the protocol, and attached this section for you. I put together a small PowerPoint presentation with 4 slides to deal with the new protocol. I would appreciate your thoughts. I have consciously made duplications for clarity, and used a common format.
Thanks for all the great input. I never heard if we got voted up, down or out, and at this point, I'm not sure that I care.
Be well
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, all Treatment and Control infants of 24 to 25 weeks will receive prophylactic surfactant. In the 26 to 27 week strata, the Control infants will receive prophylactic surfactant in the DR unless in < 30% oxygen, 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 Strata

Infants will be intubated in the delivery room and given surfactant within 30 $\pm$ 5 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 strata 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 $\geq$ 90% with an FiO2 $\leq$ 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 $\geq$ 90% with an FiO2 $\geq$ 50%

These criteria will continue in effect for 28 days from birth.

Extubation Criteria for Intubated Infants in Treatment Group: 24 – 25 weeks strata

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 $\geq$ 90% with an FiO2 $\leq$ 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 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.

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 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 30 $\pm$ 5 minutes of birth. 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

These infants will be managed on 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 Intubation (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)
- A pH <7.20 and/or 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 strata

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***. 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 provides a significant survival benefit. This approach will be used for all infants in the 24-25 wk strata, and all 26-27 week infants apart from those who require less than 30% oxygen within 15 minutes of birth. Any Control infant who has not received prophylactic surfactant in the DR, 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 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 - 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.

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 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 strata who where not intubated in the DR, will be evaluated for intubation and surfactant, and all other infants in this strata will continue to receive mechanical ventilation untill 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

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 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 $\pm$ 9.9 torr and the pH was 7.3 $\pm$ 0.1) (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 the intubation of an additional 9% of control infants compared to the current Network experience.

The Current Protocol ensures an evidence based intervention with prophylactic for all enrolled Control 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: 26 – 27 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.

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.

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
or PaCO2 < 65 torr

Control Arm

Mech Vent – 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

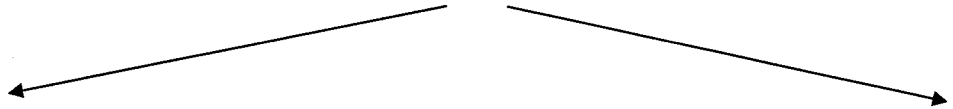
26 to 27 week Strata

Treatment	Control
Delivery Room	
DR CPAP/PEEP Intubate only for Resus	DR Prophylactic Surf < 30 ± 5 min Except if FiO2 < .30
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% pH <7.20 PaCO2 > 65 torr	FiO2 >.40 for SpO2 ≥ 90% pH < 7.25 PaCO2 > 50 torr On CPAP and FiO2 > .30

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 ANY

PaCO2 > 65 torr
pH < 7.20
FiO2 ≥ 50% for SpO2 >90%

Control
Must intubate for ANY

PaCO2 > 65 torr
pH < 7.20
FiO2 ≥ .50 for SpO2 ≥ 90%

Please note that the criteria are the same, and the difference is that the Control infants MUST be intubated if they meet any of these Criteria whereas the Treatment infants MAY be intubated if they meet any of these criteria

From:	Neil Finer
To:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Subject:	Fw: COT
Date:	Thursday, September 18, 2003 10:41:24 AM
Attachments:	COT-Schema - Steering Comm.ppt COT Revision Post Steering Comm Sept 17.doc

---

I'm resending because I'm not clear that you received these. Please review and let me have your comments
Neil
----- Original Message -----
From: Neil Finer
To: Avroy A. Fanaroff, M.D. ; Edward Donovan ; Shahnaz Duara ; Wally Carlo, M.D. ; Neil Finer ; higginsr@mail.nih.gov
Sent: Wednesday, September 17, 2003 5:49 PM
Subject: COT

Hello Everyone
I have redesigned the protocol, and attached this section for you. I put together a small PowerPoint presentation with 4 slides to deal with the new protocol. I would appreciate your thoughts. I have consciously made duplications for clarity, and used a common format.
Thanks for all the great input. I never heard if we got voted up, down or out, and at this point, I'm not sure that I care.
Be well
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
Date: Thursday, September 18, 2003 11:03:53 AM

Yes, we got them yesterday. Wally

-----Original Message-----
From: Neil Finer [mailto:nfiner@ucsd.edu]
Sent: Thursday, September 18, 2003 9:41 AM
To: Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; higginsr@mail.nih.gov
Subject: Fw: COT

I'm resending because I'm not clear that you received these. Please review and let me have your comments
Neil
----- Original Message -----
From: Neil Finer
To: Avroy A. Fanaroff, M.D. ; Edward Donovan ; Shahnaz Duara ; Wally Carlo, M.D. ; Neil Finer ; higginsr@mail.nih.gov
Sent: Wednesday, September 17, 2003 5:49 PM
Subject: COT

Hello Everyone
I have redesigned the protocol, and attached this section for you. I put together a small PowerPoint presentation with 4 slides to deal with the new protocol. I would appreciate your thoughts. I have consciously made duplications for clarity, and used a common format.
Thanks for all the great input. I never heard if we got voted up, down or out, and at this point, I'm not sure that I care.
Be well
Neil

From:	Neil Finer
To:	Wally Carlo, M.D.; Shahnaz Duara; Neil Finer; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Ed Donovan
Subject:	COT Trial
Date:	Thursday, September 25, 2003 7:52:32 PM
Attachments:	COT Schema Sept 21 03.ppt COT Post steering Comm Sept 25 Section 4.1.doc

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

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, 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 Strata

Infants will be intubated in the delivery room and given surfactant within 30 $\pm$ 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 strata ***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 $\geq$ 90% with an FiO2 $\leq$ 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 $\geq$ 90% with an FiO2 $\geq$ 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 strata

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.

Delivery Room Management : Treatment Group – 26-27 weeks 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 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. 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

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 Intubation (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 strata

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.***

<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 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 Strata 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 I have left this the same as the Treatment criteria as I suspect that during the first 28 days infants on CPAP with an FIO2 > .4 may not be intubated for that criteria alone, indeed many would not intubate for a PaCO2 of 55 at that time. I have removed the pH as I am not sure whether as a single criteria without a PaCO2 it is useful for intubation decisions. This also simplifies the protocol. How prescriptive do we want to be for the control infants and for how long? If we keep these similar to the Treatment infants we may lose any real differences, although I suspect that the big difference will be the initial extubation. The major difference as these are currently written is that a Control infant who meets both criteria MUST be intubated.
I have also added a 4 hour minimal window to allow for some flexibility. Are these too close to Treatment, will we see a difference??
I'm not sure, but some are sure to suggest that we will have to revise our Primary and increase the sample size. Any change would be a guess. This approach has never been tried in this population. It's really an Early Verder approach, in more immature infants, Verder did find differences so large that both studies were terminated early for effect!)

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 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 <u>MUST</u> be intubated if they meet <u>ANY</u> of these criteria within the first 72 hours of life.

- An FiO_2 >0.4 to maintain an indicated SpO2 $\geq$ 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 I $PaCO_2$ > 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) I Have again 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)
- 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 intubation criteria within the first 72 hours 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 < 0.40.

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.

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

Mech Vent – ***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

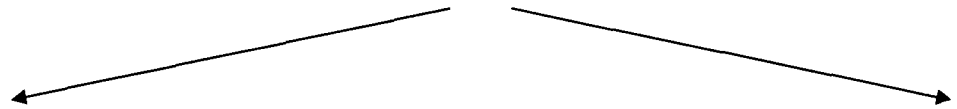
Treatment	Control
Delivery Room	
DR CPAP/PEEP Intubate only for Resus	MAY receive Prophylactic Surf
NICU	
Intubation Criteria May Intubate if meets ANY one of criteria	Control Infants not intubated in DR MUST be intubated for surfactant If meets ANY one of criteria < 72 hrs
FiO2 >.50 for SpO2 ≤ 90% PaCO2 > 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
$PaCO_2$ < 65 torr	$PaCO_2$ < 55 torr
pH > 7.20	pH > 7.25
FiO_2 <.50 for $SpO_2 \geq 90\%$	FiO_2 < .40 for $SpO_2 \geq 90\%$
MAP < 10 cm H_2O,	MAP < 8 cm H_2O,
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	Control
May Intubate if EITHER	Must intubate for EITHER if persists > 4hours
PaCO2 > 65 torr	PaCO2 > 55 torr
FiO2 ≥ 50% for SpO2 ≤90%	FiO2 ≥ .50 for SpO2 ≤ 90% (On or off CPAP)

Please note that the criteria are similar apart from a higher PaCO2 in the Control infants. Control infants MUST be intubated if they meet Either of these Criteria whereas the 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

From:	Neil Finer
To:	sshankar@med.wayne.edu; moshea@wfubmc.edu; Jon.E.Tyson@uth.tmc.edu; edward.donovan@chmcc.org; dale_phelps@urmc.rochester.edu; Richard Ehrenkranz
Cc:	Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; poo@rti.org; petrie@rti.org
Subject:	Re: Protocol review subcommittee conference calls
Date:	Sunday, August 03, 2003 3:13:08 PM
Attachments:	Response to review to Protocol Committee Aug 2 03.doc

---

Hi Richard
I am sending this to all Protocol committee members - I have added a bit about the COIN and VON trials at the end.
I know that most will not review before the phone call, but I hope that these responses are helpful.
Neil
----- Original Message -----
From: "Richard Ehrenkranz" <Richard.Ehrenkranz@yale.edu>
To: <dale_phelps@urmc.rochester.edu>; <edward.donovan@chmcc.org>; <Jon.E.Tyson@uth.tmc.edu>; <moshea@wfubmc.edu>; <nfiner@ucsd.edu>; <sshankar@med.wayne.edu>
Cc: <petrie@rti.org>; <poo@rti.org>; <higginsr@mail.nih.gov>
Sent: Monday, July 14, 2003 12:07 PM
Subject: Protocol review subcommittee conference calls

> Hi:
>
> Just a reminder about primary protocol review assignments:
>
> August 4th call: (1) COT/DR-CPAP trial-Dale, Jon and Seetha. (2) aEEG
> study-Jon and Dale
> August 18th call: (1) Inositol trial-Ed, Mike, and me. (2) ANS-ERCS
trial-
> Neil, Jon, and Seetha.
>
> Carolyn and I have sent copies of the protocols out. Neil sent his latest
> version (COT study July 3 03.doc) on July 3, 2003. Seetha will be sending
> a revised-revised version of her protocol following a Hypothermia
> subcommittee conference call on July 28th-that one will probably not be
> very different than the current one, but it will contain a budget. Let
> Carolyn or I know if you have not received copies of the protocols.
>
> Please remember to circulate your reviews before the calls. Thanks.
>
> Richard
>
>
>

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

Principle Investigator- Neil Finer, MD
Reviewer- Jon Tyson, MD, MPH
Response by Neil Finer in yellow and italics.

OVERVIEW. This is an ambitious protocol to address issues of fundamental importance to the care and outcome of ELBW infants. A factorial design would be used to assess two interventions: 1) the use of an intervention package described as early CPAP and a permissive ventilation strategy, and 2) a low oxygen saturation goal with both interventions assessed relative to a more conventional approach to care. The rationale and plan for administering and evaluating the second of these interventions are very appealing. In my judgment, however, the first intervention has major problems related to its complexity, feasibility, rationale, and evidence base. Suggestions are provided below to address this and other important issues.

SPECIFIC COMMENTS:

1. Components of first intervention ("early CPAP and a permissive ventilatory strategy"). The problems include:

A. Complexity. This intervention is difficult to describe even in a detailed protocol. It would be particularly difficult to describe in a manuscript with a methods section of acceptable length. It consists of at least 4 components (only the 1st of which was to be assessed in the pilot): systematic exposure to CPAP/PEEP in the delivery room (DR), delayed or reduced surfactant administration, more conservative intubation criteria, and more liberal extubation criteria. However, it should be reasonably feasible to administer, and each component should have reasonably strong supporting rationale and evidence of benefit. For reasons noted below, this does not seem to be the case.

B. Feasibility. Administration and assessment of this intervention package would be considerably more difficult than for the intervention in the pilot study or in the permissive hypercapnia trial which proved to be only marginally feasible at the time it was conducted in the Network. Among other problems, the requirement for availability of study personnel and equipment (exclusion criteria on page 10) would predictably limit enrollment, particularly at nights and on weekends. Unless this intervention package is simplified, I think the study will fail.

C. Rationale and Evidence Base. For the following reasons, the trial could be simplified and strengthened if CPAP and prophylactic surfactant were provided to both groups rather than only the intervention group:

1) CPAP/PEEP –The reason that continuous distending pressure has not been systematically recommended and used in the DR has been the lack of a

satisfactory method for administration in that setting rather than concerns that it would not be beneficial in this setting.

On what basis is this statement made? In Europe and in some USA centers, ventilators are placed in the DR which can easily deliver CPAP. Columbia makes their own apparatus, and many other centers have utilized different devices including the Neopuff which has been FDA approved for some time. I believe that CPAP is not used in the DR for a number of reasons – It is never discussed in any current resuscitation guidelines. There are no prospective studies of its use in the DR. The resuscitation teams do not include the delivery of CPAP/PEEP as a therapeutic intervention. In some Network centers including our own CPAP/PEEP is an intervention which is utilized in all resuscitation requiring positive pressure support, or for the ELBW infant.

The use of continuous distending pressure for VLBW infants in the NICU is well supported by randomized trials (see Cochrane review by Ho et al). Depending on the equipment used in the DR (anesthesia bags, self inflating bags, etc) and the skill of the operator, continuous distending pressure has been variably used in the DR. The pilot study showed the feasibility of reliably administering distending pressure in the DR. In the absence of evidence or even rationale to the contrary, there does not seem to be a good reason to forego use of continuous distending pressure in the DR in the control group. That said, there is not good rationale or data to show that it can not be briefly interrupted to administer surfactant in the DR or in the NICU (or that ventilation should not be provided as needed to regulate PaCO2). The use of CPAP might be beneficial if it is used in a way that does not delay or reduce surfactant use but not beneficial (or even harmful) if it does.

2) Surfactant use. Surfactant administration is one of only a few interventions in all of perinatal medicine that has been demonstrated in randomized trials to substantially reduce mortality. The reduction in mortality achieved with use of rescue surfactant (relative to no surfactant) is further reduced by administration of prophylactic surfactant. The Cochrane review of prophylactic surfactant (vs. selective use of surfactant) identified a relative risk of 0.61 for mortality. A reduction in pneumothorax (relative risk = 0.62) and in either death or bronchopulmonary dysplasia (relative risk = 0.85) was also identified along with a trend toward less Grade 3 or 4 ICH (relative risk = 0.84). The multicenter trial by Kendig et al (with Dale Phelps as the senior author) showed that prophylactic surfactant could be delayed to 10 minutes of age without discernible effect on the outcome of infants 24-28 weeks gestationThis was emphasized in the October 2001 protocol for the pilot study, and I have not found any clinical trials to show that further delay would not compromise outcome.

(The meta analyses for this intervention included surfactant being given up to 15 minutes (Walti 1995).)

Given the existing evidence about surfactant prophylaxis, it would not be justified to undertake a large and expensive multicenter trial of an intervention that would delay and reduce surfactant prophylaxis unless single center

randomized trials had suggested better outcomes than achieved with surfactant prophylaxis.

There are no studies that have compared CPAP initiated in the DR with prophylactic surfactant. Prophylactic surfactant requires that infants receive treatment who may not require this, and prophylaxis has not been compared to early treatment. In the Cochrane review of Early surfactant vs delayed selective, (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, these authors made the following comments which I believe are germane to this discussion. "Despite evidence supporting the efficacy of prophylactic and early surfactant therapy, estimates show that not all infants judged to be at high risk for RDS are surfactant deficient. Of the trials included in this meta-analysis, only Konishi (1992) estimated surfactant deficiency prior to surfactant administration. He found only 66% of those judged at risk for RDS based on a birth weight criterion of 500 - 1500 grams to have surfactant deficiency at birth. Kattwinkel (1993) noted that of those randomized to early selective surfactant treatment only 43% of 621 infants required surfactant as indicated by their admittedly liberal criteria. Clearly prophylaxis with surfactant would overtreat a large number of infants judged at risk for RDS, and this overtreatment may be justified to save the life of every 20th child. It appears, however, that treatment with surfactant within the first two hours of life in those infants intubated for respiratory distress confers the benefits of reduced mortality and pneumothorax while treating a substantially smaller portion of those infants judged at risk prenatally." It is hard to judge the relative value of early surfactant treatment compared to true prophylactic use of surfactant in the absence of any randomized trials that have directly compared these policies. Prophylactic rather than delayed administration of surfactant to all infants deemed at high risk for RDS reduces the risk of pneumothorax, pulmonary interstitial emphysema, bronchopulmonary dysplasia or death, as well as mortality (Soll 1999). Similar benefits are associated with early selective rather than delayed surfactant administration in premature infants intubated for respiratory distress within the first two hours of life. With prophylactic rather than delayed surfactant, the number of infants that would need to be treated to avoid one pneumothorax was 50, and only 20 to prevent one death; the present meta-analysis suggests that with early rather than delayed surfactant treatment, 20 infants need be treated to prevent one pneumothorax, and 35 to prevent one neonatal death. Thus providing surfactant within 2 hours of birth provides a significant benefit, and when considering the risks of treating infants who may not require such treatment, may be a better alternative. In addition, this option is evidence based and allows the Treated group to receive the surfactant benefit within an early time period. We believe that the benefit of CPAP from birth may be as significant as the receipt of prophylactic surfactant.

In addition, there are few studies that have compared prophylactic with early rescue, and the results of giving early surfactant within 2 hours of birth still show significant benefit. In addition, no-one at present advocates CPAP/PEEP in the DR and denying that this is the current reality is also not evidence based.

The trial is currently designed to avoid or delay use of not only surfactant prophylaxis but also rescue surfactant in the intervention group. The intervention group could not be intubated in the DR solely for surfactant administration, surfactant use would not be required among those who were intubated, and the intubation criteria in the NICU would delay surfactant administration there (relative to the intervention group, to clinical practice in most centers, and to use of surfactant in trials demonstrating the value of rescue vs. no surfactant).

The evidence that supports these design features comes only from methodologically weak observational studies—most notably, a cross-sectional survey reporting a relatively low rate of CLD in one prominent center (Columbia) which differed from comparison centers in a myriad of ways beside surfactant use. In the best study to date comparing this center to other centers, Van Marter et al concluded that the relatively low rate of CLD was better explained by use of less mechanical ventilation than by any of a large number of other factors assessed, including surfactant therapy.

This an interesting position on this previous publication wherein one unit does apply CPAP in the DR. It is methodologically weak, but it is also the only data from this country that has been published on the use of CPAP in the DR. The previous position that CPAP is not used in the DR because of lack of equipment, obviously does not include Columbia. The highest Odds Ratio for CLD was the use of ventilation on the first day of life in the Van Marter study. I quote from their study "In multivariate logistic regression analyses, the initiation of mechanical ventilation was associated with increased risk of CLD: after adjusting for other potential confounding factors, the odds ratios for mechanical ventilation were 13.4 on day of birth, 9.6 on days 1 to 3, and 6.3 on days 4 to 7" Moreover, the analyses of the randomized pilot study in the Network have provided no evidence of benefit from the delivery room intervention, a finding that may be due either to a delay in giving surfactant or simply a lack of much benefit from administering CPAP in the DR.

This study was not powered to look at the benefit of DR CPAP as all infants received subsequent CPAP in the NICU, and thus the groups may have differed by as little as 5-10 minutes of CPAP in the DR. The power was further reduced as 45% of the infants were intubated in the DR. You cannot use these results to negate the potential benefit of DR CPAP compared with a different intervention such as prophylactic surfactant. The current study will not include infants of 23 weeks who represented most of the deaths in the DR CPAP feasibility trial, a design issue emanating from that study. If there were better support for the use of early CPAP, one could also argue that our study is not justified. This seems like a no win approach. Many are concerned that early, ie DR CPAP may be a better intervention, and needs to be compared with prophylactic or early CPAP In addition the studies of Verder et al did not utilize DR CPAP but found significant benefit when surfactant was given early, but not within 10-15 minutes. Prophylactic treatment also treats infants who may not require intubation, and this cost needs to be considered as this is not a benign

intervention. Either way, the findings do not support the need for a trial in which infants were randomized to receive the DR intervention as the trial is currently designed.

Thus, there is not the evidence base to justify a large multicenter trial in which surfactant prophylaxis would be delayed or reduced.

I completely disagree. We may not do this study, but this approach is being taken by Morley et al in Australia, and if we delay, then the evidence that we lack will be provided, and we will have missed an opportunity.

The NICHD can do such a study, and follow-up these infants, and this study is needed, and the lack of current evidence is one of the reasons that we need to do such a trial. I would again emphasize that one cannot use the evidence of prophylaxis which was not obtained in trials which compared prophylaxis with early CPAP to conclude that prophylactic surfactant is superior to early CPAP. Our Ventilation group believes this to be the situation, and some currently provide early DR CPAP and attempt to avoid surfactant, in spite of the lack of good evidence that early CPAP is a proven benefit. We believe that many other units have also changed their practices in this direction, and if we or others do not get such evidence, practice may continue to change in this direction.

I believe that we may be able to provide prophylactic surfactant to all as suggested below and continue with the aggressive versus conservative weaning as suggested by Jon. This approach will result in our study failing to evaluate whether DR CPAP is a beneficial support for the ELBW infant. That will result in no evidence for DR CPAP and the continuance of current empirical practices!!!

Suggestions for modifying this arm of the trial:

A. For all the above reasons, provide continuous distending airway pressure (***not a currently proven intervention and never will be without such a trial)*** and routinely provide prophylactic surfactant by 10 minutes of age to all infants in the trial. (An argument could be made to forego prophylactic surfactant therapy for the small proportion of infants who do not appear to need oxygen in the DR at 10 minutes age.) Surfactant might be administered using a side port to the ET tube adapter so that distending pressure could be provided while surfactant was being administered (a feature that would appeal to the staunchest CPAP advocates).

The problem here is that while using early CPAP, all infants get intubated in the DR, not necessarily the ideal approach, and we never test whether early CPAP and a permissive approach can avoid intubation and result in improved outcomes. This study population is now more likely to benefit as we have removed infants of 23 weeks, who will require intubation for resuscitation. To avoid overdistention of the lung, recommendations could be provided for the initial airway pressures as already noted in the protocol for the Neopuff (or other resuscitation devices allowed).

B. Conceptualize and design this arm of the trial as a trial of conservative use of mechanical ventilation. ***Is this now a repeat trial of permissive***

hypercapnia?? Randomize infants on admission to the NICU to the remaining 2 components of the intervention package (conservative intubation criteria and liberal extubation criteria). Infants in the intervention group who were intubated solely for surfactant administration in the DR could be quickly extubated in the NICU (within 10-60 minutes of intubation using criteria already defined on page 12 of the current protocol).

We can do this. The real question is should we, and is this a more informative and relevant strategy? There is nothing simple about caring for an ELBW infant. Requiring intubation in the DR may cause more morbidity than not, a finding that will never be determined if all are intubated. Besides, how do you explain the fact that Columbia and others can avoid surfactant in such infants without a cost in terms of death or CLD. Agreed that these are not rigorous prospective observations, but they also should not be totally ignored, especially their CLD rates. Seems that we are throwing the baby out with the bathwater here.They could be reintubated using conservative criteria (like those on the top of page 12).

This design modification would have multiple advantages: 1) It would be unnecessary to require research personnel to be present in the DR and would allow enrollment at all hours;

Research personnel don't have to be in the DR – They weren't for DR CPAP. The staff would know the randomization and then proceed - Control- intubate for prophylactic surfactant and Treatment - CPAP, evaluate for early surf and then try to avoid the ventilator. Lets not make this more complicated than it is. Some centers already do something like this.2) Infants who could not be resuscitated or who were not resuscitated because they were smaller or less mature than anticipated could be excluded; ***They are included and evaluated, a truer test! We have removed the 23 weekers***. 3) There would be no ambiguity in every infants enrolled, a problem likely to occur with the current design;

Why – what's ambiguous about intubation for surfactant versus CPAP?? Treatment infants who require intubation for resus will receive surfactant as soon as possible following stabilization. 4) The enrollment rate and duration of study could be more accurately estimated; ***We can already estimate the number of infants in these groups and they currently receive surfactant > 90% of the time.***5) Protocol violations would be less difficult to evaluate;***Its easy to determine if a Treated infant was intubated in the DR – the only hard part is to determine if it was for resuscitation and I believe that the team knows this – they should.*** 6) There would be no ethical concerns about withholding prophylactic surfactant as an intervention known to reduce mortality.

We already are comfortable that early CPAP may be an equivalent or better intervention and have the equipoise necessary to proceed. If we wait for the ultimate data that CPAP is better, we don't need thus study. That I believe is the major issue. Do we ask a question that needs answering that is relevant to current care, or do we wait for better data to show that it is really a better intervention and avoid this study because it is too difficult.??

It is not too difficult; it is a challenge but not an ethical one. The timing for asking this question is now!! The evidence is not perfect, the suggestion is there, the Network is the best group to do this, and Neonatology is waiting for this answer!! Revised in this way, the trial would be much simpler, less expensive and labor intensive, more feasible, and more easily described than the proposed study.

C. Be more specific about the regulation of ventilation for the two groups. If this is not done, the intervention that is assessed may well vary across centers in an important way. An issue in comparing conventional vs. use of mechanical ventilation is whether indications should be specified not only for intubation and extubation but also for increasing or decreasing ventilation in the two groups (with different PaCO2 threshold levels in the two groups). If one believes that mechanical ventilation increases the risk of CLD only because of the presence of the endotracheal tube, ***The duration of mechanical ventilation is a predictive factor in the occurrence of CLD – however most of these observations are not from prospective trials should we ignore them??? it doesn't matter how the infants are ventilated. It matters for how long!!*** However, this doesn't seem plausible, and the prior Network trial, the Cochrane review, and the trials in adults provide some evidence that allowing higher PaCO2 values during mechanical ventilation might reduce the incidence of CLD.

This evidence is at best weak in Neonatology. In addition if you really want to get complicated start designing a protocol to make ventilator changes in response to certain blood gases. Extubation may be as much about expectation as it is about science and lab data. If you believe that the infant can be extubated you will try, if not you won't and you will user the blood gases to justify your position, not the reverse. If there aren't higher PaCO2 thresholds for increasing ventilation in the conservative ventilation group, we risk the inconsistency of accepting PaCO2s when infants are not ventilated (with PaCO2 values as high as 60 torr considered acceptable) than when they are ventilated (when, depending on the views of the attending, PaCO2 values might be maintained in the low 40s). This doesn't seem appropriate for an intervention intended to minimize mechanical ventilation.

In making the above suggestion, I have deliberately used the words "PaCO2 thresholds" rather than "PaCO2 goals" or "goal range." This would help to avoid designating the caregivers to be noncompliant when ventilator changes are made per protocol but the PaCO2 values remained outside a "goal range" due to the infant's spontaneous respirations. Whether or not the mean PaCO2 differed between the two groups, the issue should be whether the intervention group received less ventilatory support. While this may seem a small point, I think this problem prompted some misinterpretation and unwarranted criticism of the hypothermia trial that we would want to be sure to avoid in this trial.)

I would suggest that if we want to change anything here, that we agree to measure tidal volumes in the treated group and ensure that they are < 5-6 ml/kg – Now that would be neat and doable!! We do not know that PaCO2 is the correct lead indicator – what if it is volutrauma and the PaCO2 is a follower – Never been evaluated!!

D. Consider increasing the treatment difference between groups by making the criteria for intubation of the treatment group by 1) increasing the threshold FiO2 criterion for intubation of the intervention group in the NICU higher (perhaps as high as 0.8, a number still lower than what the Columbia group would advocate)

I'm not sure that Columbia does this for infants < 25 weeks, and they have never even published this data – now we are going to change the protocol to an even more extreme difference for which there is absolutely NO data – How would you defend this to your IRB? What evidence would you submit in support – At least Van Marter published a paper that was peer reviewed!! and/or b) lowering the threshold pH from 7.20 to 7.15, a value that may still be higher than what the Columbia group would accept. ***We don't know what they would accept for any specific population. When I shared the DR CPAP feasibility trial results with Richard Polin he believed that they also intubated most of their 23 week infants – did we get that from the literature???***

2. Second intervention. The measures to bind the caregivers to oxygen saturation group and document the values actually achieved are very appealing. However, I have some questions: What kind of information will the manufacturers provide to assure that the recalibrated monitors function as intended? We will be evaluating and comparing the actual values with unaltered devices in a preliminary evaluation if this trial proceeds. ***Masimo has agreed to provide about 10-20 of these devices for evaluation without charge***. Should any (small) reliability studies be done to verify that the monitors are reliable or that these monitors do not differ systematically from some other brand(s) commonly used in NICUs?

These studies have already been done and each manufacturer's device is not identical to the others but the systematic bias is small. The Masimo was the best device tested (with a mean difference between actual measured SaO2 and SpO2 of 0.06(+2.5)%. Bohnhorst, B.; Peter, C. S., and Poets, C. F. Detection of hyperoxaemia in neonates: data from three new pulse oximeters. Arch Dis Child Fetal Neonatal Ed. 2002 Nov; 87(3):F217-9. and besides it is almost impossible to determine the correct SaO2 value without a cuvette determination using a blood sample of actual SaO2 as prediction is virtually impossible from the PaO2. What should be done to assure that false low oxygen saturation values (due to a loose probe) will be correctly identified in evaluating the stored achieved SpO2 values? ***A review of the actual data is often revealing – but why should we correct since that Masimo has the best motion artifact rejection available, the data we currently use is much more contaminated. We are looking at the stored values for the achievable ranges – not a specific set of values – are we able to produce two distinct levels of SpO2?***? Because SpO2 may be less stable off the ventilator than on, because ROP may be influenced by SpO2 off the ventilator as well as on, and because the groups will differ in mechanical ventilation, why not obtain SpO2 readings at the same ages irrespective of

mechanical ventilation (until they are off oxygen ***The current protocol indicates that the monitors will continue till off oxygen.–***

The current protocol states that we will obtain 72 hours of PO data every week till the infant is off of oxygen, quoted below from p 16- COT protocol.

"At 3 days and every subsequent 7 days till the infant is no longer receiving ventilatory support or oxygen, the stored actual SaO2 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."

or perhaps in less than say an FiO2 of 0.25)? Shouldn't oxygen saturation be obtained on day 1 as well as at the later ages?

3. Primary Hypotheses. This section is necessarily more complex than in most Network studies because of the factorial design and because interactions are a particularly important issue in such a trial.

The first two hypotheses address the main effect of one of the interventions on an outcome. Whether or not there is an interaction other intervention is not addressed. ***This has been discussed with Ken and he agrees with the revised wording – we can further discuss.***

The 3rd hypothesis appears to address an interaction without specifying a main effect for either variable. Also it is unclear which cell or cells the "Early CPAP and high SpO2 cell" is being compared. The basis for this hypothesis (that survival without severe impairment is increased with both two interventions) is also unclear and doesn't seem to be addressed elsewhere in the protocol. ***There is no data that has combined these 2 intervention s but the combination of Columbia data and the observations of Tin et al and Chow et al, allow us to suggest this possibility – that's all there is – there will be no more till we or others ask the questions!***

Interactions and their description and interpretation are often confusing to clinicians, particularly when logistic regression analyses are performed (as they would be for this trial. This requires an understanding of interactions on a multiplicative scale.) To help specify and communicate your hypotheses, I'd suggest a) provide a 2 x 2 table structured like the table in the study design section and fill in the expected percentage of infants in each of the cells who have CLD. (Alternatively you could simply an "x" to indicate the expected % of babies with CLD in cell a (the early CPAP + high SpO2" cell which is anticipated to have the lowest % with CLD) and then insert a multiple of x to indicate the expected incidence in each of the other cells); b) Also provide a similar table to communicate your hypotheses for the other two major outcome variables--survival without severe ROP & survival without impairment at 18-22 months. ***We can certainly do this!***

Is increased survival without impairment really justified and necessary as a primary hypothesis*? Currently we believe that the study will be powered for the other 2 questions with sufficient power to hopefully address this important question .I have discussed in detail with Ken and we have previously tried to answer this comment.* There is little evidence provided in the introduction to justify this conclusion, and it has been very difficult to show improved survival without impairment in testing any neonatal intervention to date. *(Even for surfactant where none of the trials hypothesized that the long term outcomes would be a primary outcome!)* An increase in survival without CLD or severe ROP would be compelling evidence of benefit provided survival without impairment is not decreased. One would only need to test the hypothesis that survival without impairment is not reduced (which might require only a one-tailed test and allow a smaller sample size at a given power). *Agreed!!* As was done in the early steroid-permissive hypercapnia trial, the sample size for the study could be adjusted to rule out a clinically important reduction in survival without impairment. This would not require that survival without impairment be a primary outcome or the outcome of a primary hypothesis. Currently it is not listed as a primary outcome, and a primary hypothesis addressing survival without impairment would require that the publication of trial results be delayed approximately two years. *We agree here, and will leave the primaries as ROP and CLD relative to two interventions.*

4. Secondary Hypotheses. As written there are 3 interventions ("CPAP"; low SpO2; and both) and at least 18 or more outcome variables, for at least 48 comparisons (not counting the additional comparisons for the primary hypotheses). This causes a big problem with multiple comparisons. How this problem will be addressed should be specified in the statistics section. (While there is no perfect solution, requiring a $p<0.01$ would be a reasonable option). (If you accept the above suggestions for providing DR CPAP and surfactant to all of the infants, intervention, you can reduce the problem somewhat by removing the 1st and 3rd outcome variables*.) I will ask Ken to consider this.*

5. Population. GA is only one factor in considering whether to give intensive care to the smallest infants, in part because the best obstetric estimates of gestational age are commonly in error. Among the lowest estimates of GA, the direction of that error tends toward underestimating GA. As long as mechanical ventilation is to be provided, it is unclear that infants who are 23 weeks by best Ob. GA (or even lower estimates) should be excluded for either the current protocol or a revised protocol. Unless the primary interest were the effect of early CPAP (rather than continuous distending pressure administered as *either* CPAP or PEEP), the almost universal need for intubation in the DR is not a compelling reason to exclude these infants. The outcome of the most immature infants is of great interest, and a high rate of adverse outcomes is usually an argument for inclusion unless the patients are thought to be unresponsive to the intervention. If the protocol is revised as suggested, the arguments raised for excluding these

infants would be weaker, in part because those who were considered nonviable or who died in the DR could be excluded.
We believe that the universal need for DR Intubation combined with a > 70% mortality for the 23 week infants effectively removes the ability to evaluate DR CPAP. Yes if we were giving prophylactic surfactant for all, they could be included, but we believe that evaluating DR CPAP is important. Few of these infants actually die in the DR, and once enrolled they would be included in an intent to treat analysis.

6. Inclusion criteria. Will multiple births be included? ***Yes, and we agree.*** There are now appropriate statistical techniques to allow randomization could be done in such a way that both twins can be included in the same treatment group.

7. Exclusion criteria. If survival without impairment is to be a primary or important outcome, shouldn't infants thought unlikely to attend the follow-up clinic at 18 months (including infants of mothers who plan to move from the area)? ***We agree that this will not be the Primary.***

8. Randomization. See above regarding randomization on admission to the NICU and about inclusion of multiple births. Stratification by center should be noted.

9. Outcome measures. The stated primary outcome measure is literally what was intended. There are either two or three primary outcome measures.

10. Assessment of Outcomes and Care. See above comments about SpO2 monitoring. What will be done to assure the reliable and accurate collection of ROP data? I understand that these data have not been well collected in the Network in the past. ***I am not aware of the specific issues regarding the Network data for ROP. I would be pleased to be so educated.***

If the DR components are included, would there be videotaping in a sample (preferably random) of infants. ***There could be – we would have to determine the purpose of such videotaping – to ensure compliance – but if only a few centers do this will their observations be generalizable?***

11. Adverse Events and Resuscitation Associated Events. If the above suggestions are accepted, this can be simplified by removing air leak on admission and need for chest compressions and/or epi in the DR. and the resuscitation associated events. ***I'm unclear why we would not want to look at these if the study represents a change in practice – these events may be related to the interventions be they CPAP or intubation.***

12. Statistical Analyses. As I understand the study, the appropriate primary analyses for each of the 3 main outcomes (survival without CLD, survival without

severe ROP, survival without impairment) would be a logistic regression analysis that included a term for each of the interventions and an interaction term.

See above comments about multiple ***analyses I have discussed with Ken and will refer this to him.***

13. Sample size. The assessment of interaction needs to be better addressed. However, for reasons that should be discussed, it is not clear that an increase in sample size is necessarily warranted. ***Will do as above***

14. Duration of study. These need to be specifically addressed with careful consideration of refusal of consent and exclusion of infants (particularly if there is a requirement for research staff in the DR).

15. Budget. This needs to be specified and tabulated for all important costs, including any costs for research personnel in the DR. ***We do not believe that research staff are required in the DR, as consent will be obtained prior to delivery. The coordinator or an alternate can randomize and instruct regarding the PO that is to be used for this infant. These will all have a unique label, which will be utilized to select the actual PO.***
We will certainly prepare a detailed budget. Our major cost will be the actual Pos which will cost about $2000.00 per device for approximately 200 of these, plus the data collection at about 15-20 hours per patient. If we decide to go with the Neopuffs, F-P may provide or we may purchase. I will prepare a detailed budget once we are clear on the design.

Final Comments: I appreciate the detailed review. We all want to determine the best initial and ongoing approach for the ELBW infant.
This study is complex but doable within the Network. It will be the first to look at the combination of controlling SpO2 from birth and evaluating a more permissive approach to determine if there is a role for early CPAP. We have allowed that the CPAP infants may be intubated and receive surfactant within 30 minutes of birth – this is somewhat later than the prophylactic trials and probably earlier than most early trials, but allows the limitation of surfactant top infants who may not need it – This will be a difference from the controls, almost all of whom will get prophylactic surf. This may help in comparing prophylactic versus early for this population and indicate how many infants do not need surfactant in this population. In addition there is one ongoing trial the COIN trial (apparently having difficulty enrolling their target of 600 infants which should have been complete by Jan 2003 according to their initial estimates.) – this trial is evaluating early CPAP versus intubation. They did a pilot and demonstrated that less infants in the CPAP arm required subsequent intubation
'I have detailed their inclusion criteria below:

COIN Trial Enrolment criteria:

1. The infant has no known abnormality or condition that might have an adverse effect on breathing or ventilation from birth apart from prematurity.
2. The infant is born in a level three hospital participating in the trial.
3. The gestation of the infant is between ***25 weeks' and 28 weeks' 6 days*** by the best obstetric calculation.
4. The infant breathes spontaneously at birth, or after assistance with hand bagging, but needs respiratory support because he or she has one or more of the following:
   a. recession (retraction) of the lower ribs or sternum,
   b. grunting respiration,
   c. a need for increased inspired oxygen.

The gestational age range 25-28 weeks was been chosen because in the three years 1996-1998 in the Royal Women's Hospital, Melbourne, over 95% of infants at these gestations have been intubated with an endotracheal tube and ventilated from birth.

Treatment allocation

Treatment allocation will be either to nasal CPAP at 8 cm H_2O, or to intubation and IPPV. Allocation will be assigned randomly, using a random number generator and permuted blocks for each centre. This will be produced by the statistical department of the Royal Children's Hospital. Randomisation will be stratified into two gestational age groups: 25 and 26 weeks', and 27 and 28 weeks'. This will reduce any imbalance in gestational age between the groups and allow analysis of the groups separately. The assigned treatment will be enclosed in sequentially numbered opaque envelopes. There will be a separate set of envelopes for each gestational age stratum in each centre. The randomisation envelopes will be available near the resuscitation trolley used for preterm infants.

In the first few minutes after the birth the doctor has to decide whether the infant is going to breathe or need intubating immediately because of apnoea. ***This trial only enrols infants who are breathing soon after birth***. Therefore, only when it is seen that the infant is breathing by 5 minutes of age should the randomisation envelope be opened. The allocated treatment will then be started immediately.

In the rare situation where an infant who is eligible for the study is randomised to ventilation but the doctor does not want to ventilate the infant because he is breathing normally in air then that infant need not be ventilated. However, if respiratory support is required subsequently, this must be provided via an endotracheal tube rather than nasal CPAP.

Please note that this trial differs from our design in the following areas _
Network Study will enrol infants from 24 to 27 weeks vs 25 to 28 wks
COIN will evaluate for spontaneous breathing and if not present – infant not enrolled – Our study will enrol all, and once intubated treatment infants will be rapidly weaned. Our study will be informative about treating all infants – COIN will leave management of those infants not effectively breathing out of protocol.
COIN will not offer an early window for surfactant to their CPAP infants - Network will.
COIN criteria for intubation of CPAP infants:

Indications for initiating ventilation for infants randomised to nasal CPAP

Infants randomised to nasal CPAP should be ventilated **only** if they fulfil the any of the following criteria:

1) They develop apnoea which is unresponsive to stimulation or other treatment and is either

a) *frequent*: greater than 6 episodes in six hours requiring stimulation or

b) *severe*: more than one episode requiring positive pressure ventilation.

2) They have an arterial pH below 7.25 with a $PaCO_2$ above 60 mmHg, or untreatable metabolic acidosis.

3) They require an inspired oxygen concentration greater than 60% to maintain oxygen saturation above 90%.

4) They required an anaesthetic.

Once enrolled in the trial they **must not be ventilated outside these criteria**.

Both studies believe that early CPAP may be an effective alternate to prophylactic surfactant – COIN does not mention the use of surfactant and will analyze number of does given, but its use is not protocolized.
The VON is initiating a 3 arm trial to compare Early CPAP, Intubation with surfactant and extubation and prophylactic surfactant and CMV.

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: Re: Columbia CPAP
Date: Friday, August 08, 2003 7:39:40 PM

Jon
Is this data better than the Van Marter data?
Neil

----- Original Message -----
From: Jon E Tyson
To: Neil N Finer ; higginsr@mail.nih.gov ; Richard Ehrenkranz (richard.ehrenkranz) ; Dale Phelps MD ; Seetha Shankaran (s_shankaran) ; Michael O'Shea
Cc: Kennedy Kathleen A ; Moya Fernando R
Sent: Thursday, August 07, 2003 1:48 PM
Subject: FW: Columbia CPAP

For reasons unrelated to the Network, I spoke with Jack Lorenz who is at Columbia. In the course of that conversation, I indicated that the Network was considering a trial assessing all or some of the components of the methods used at Columbia to reduce CLD. Being uncertain about exactly what the "Columbia method" is, I asked him what he thought was the best published information about the intubation criteria used there. His answer (initial e mail below) indicates disparity within the group but the lower published FiO2 requirement is higher than in our intervention group.

-----Original Message-----
From: J.M. Lorenz, MD [mailto:jl1084@columbia.edu]
Sent: Thursday, August 07, 2003 8:08 AM
To: Tyson, Jon E
Subject: Re: Columbia CPAP

> Other criteria for intubation are pCO2 > 65, severe retractions on CPAP, and apnea.(These are delineated in the first paper). Our criteria for extubation are IMV rate 15/min, pCO2 50-60 mmHg, and pO2 50-70 mmHg with FiO2 < 40%. Usually at the time of extubation, PIP is 18-20 (we rarely use less than this!). If the baby is on pressure control/pressure support, the later is usual 10 at extubation. These criteria are not followed as closely as the criteria for intubation -- it depends whethet it's during the day or at night and how busy the unit is.

Jon E Tyson wrote:

Thanks! Are there PaCO2 criteria if the infant does not meet the FiO2 requirement for intubation? Are there consistent and clearly described criteria for extubation?

> -----Original Message-----
> **From:** J.M. Lorenz, MD [mailto:jl1084@columbia.edu]
> **Sent:** Wednesday, August 06, 2003 12:55 PM
> **To:** Jon Tyson
> **Subject:** Columbia CPAP

The best reference for the nuts and bolts of how we use CPAP, the indications with CPAP, and our experience before and after the introduction of surfactant is in Sahni R and Wung JT. Continuous positive airway pressure (CPAP). Indian J Pediatr 1998; 65: 265-271. If this reference is not conveniently available, I'd be happy to fax it to you. Polin RA and Sahni R. Newer experience with CPAP. Semin Neonatol 2002; 7:370-389 updates the experience. You'll note some disagreement about what oxygen requirement is an indication for intubation: the criteria in the first paper is " P_aO_2 < 50 mm HG while breathing 80-100% oxygen," while the in the second it's "oxygenation is worsening or inadequate with F_iO_2 > 0.60". This is not a change over time; it's a *disagreement*. Also note that the proportion of infants who are ventilated and receive surfactant has increased from 1900-1993 to 1998-2000, without an increase in O2 requirement at 36 wk PMA. RAP arrived in 1998.

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 Table
Date:	Tuesday, August 12, 2003 7:36:24 PM
Attachments:	Table of COT Aug 12 03.doc

This is what the Table would look like if we give Surf to all the 24-25 wks strata and to all above except those that are in room air by 15 minutes.
I increased the PaCO2 to 65 for the Treatment infants.
What do you think?
Neil

Comparison of COT Study Groups

Group Assignment --- **Interventions**	**Treatment Group**	**Conventional Management**
Initial DR care	Start CPAP(or PPV w/PEEP if needed) with resuscitation CPAP/PEEP 7-8 cm (PIP 15 cm)	Conventional resuscitation procedure-it is anticipated that 50% of these infants will be intubated in the DR
Surfactant Administration within 15 min for all 24 – 25 wks And for all 26-27 weeks unless in room air by 15 min	24-25 wks GA: Administer surfactant w/in 15 min of age 26-27 wks GA: Administer surfactant w/in 15 min of age if $FiO_2 > 0.21$ Evaluate promptly for extubation w/in 60 min to CPAP or NSIM If not attempted, must be attempted w/in 12 $\pm$ 2 hrs (see Extubation criteria below)	24-25 wks GA: Administer surfactant w/in 15 min of age 26-27 wks GA: Administer surfactant w/in 15 min of age if $FiO_2 > 0.21$
Not Intubated in the DR & Transferred to NICU Non-intubated ***Only for 26-27 week infants in Room air by 15 minutes***	Continue CPAP May be Intubated **<u>if any</u>** of the following present (minimum criteria): FiO2 >0.50 for $SpO_2 \geq$ 88% pH < 7.20 and/or $PaCO_2$ >65 Apnea needing BMV Shock/sepsis/surgery, etc	**<u>Must</u>** Intubate & administer surfactant **<u>if any</u>** of the following criteria are met: $FiO_2 > 0.40$ for $SpO_2 \leq 88\%$ Use of CPAP pH <7.25 &/or $PaCO_2$ >50 Apnea needing BMV Shock/sepsis/surgery, etc
Extubation Criteria (in effect for at least 28 days from birth)	**<u>Must</u>** Extubate w/in 12 hrs if **<u>ALL</u>** criteria below are met: $PaCO_2$ < 65 with pH > 7.20 $SpO_2 \geq 90\%$ with $FiO_2 \leq 0.50$ MAP < 10, IMV <15 (or amplitude <2x MAP if on HFV)	Extubation **<u>may be attempted</u>** only if meet **<u>ALL</u>** of the criteria are met: $PaCO_2$ <50 &/or pH >7.25 $FiO_2 < 0.40$ w/$SpO_2 > 88\%$ MAP < 8, IMV <15 (or amplitude <2x MAP if on HFV)
Oximetry	Study pulse oximeter until in RA or off ventilatory support or CPAP for 72 hrs	Study pulse oximeter until in RA or off ventilatory support or CPAP for 72 hrs

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 Table
Date:	Wednesday, August 13, 2003 12:46:14 PM

Looks OK. We still need to do what ever it takes to guarantee "buy-in". In our previous trials, we enrolled (buy-in type 1) but then were unable to comply with the study intervention strategies (buy-in type 2).

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 7:36:54 PM >>>
This is what the Table would look like if we give Surf to all the 24-25 wks strata and to all above except those that are in room air by 15 minutes.
I increased the PaCO2 to 65 for the Treatment infants.
What do you think?
Neil

From: Neil Finer
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: DR CPAP
Date: Thursday, August 14, 2003 2:12:55 PM

This will be fine - We need to agree on the protocol, and then I can produce the presentation.
Talk to you tomorrow.
Neil

----- Original Message -----
From: Higgins, Rosemary (NIH/NICHD)
To: Neil Finer (E-mail)
Sent: Thursday, August 14, 2003 10:55 AM
Subject: DR CPAP

Neil
It may be helpful when you resubmit the protocol for Steering Committee appraisal if you include a short power point slide presentation that the PIs can use at their sites. What do you think>?
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:	Avroy A. Fanaroff, M.D.; Edward Donovan; Shahnaz Duara; Wally Carlo, M.D.; Neil Finer; Higgins, Rosemary (NIH/NICHD)
Cc:	Poole, W. Kenneth
Subject:	COT Protocol
Date:	Friday, August 15, 2003 4:34:41 PM
Attachments:	COT study Aug 15 03.doc

Hello All
Here is the current version which I hope includes today's comments.
Major changes =
inclusion of current VON data from SPR - Note that they showed a reduction of IVH and severe IVH in earlier treated infants and thus my question of whether we really had is right on the first go-round - is 30 minutes a better time to assess for surf administration?
Some edits to address some concerns raised by Dale and Richard.
Be well
Talk to you on Tuesday morning
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/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 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). While 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).[27] These observations support earlier than later use of surfactant.

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.[293031] 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 < 1000gm, 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.

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 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 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 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

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 15 minutes following delivery, they will be intubated at that time and receive surfactant

At 60 (should this be 30 min as in the original protocol – The VON trial shows less IVH in earlier treated??) minutes of life all non-intubated Treatment infants will be evaluated for surfactant treatment, and receive surfactant if they require an FiO2 >0.5 to maintain an indicated SpO2 > 88% (using the altered Pulse Oximeters)

Extubation must be attempted within 12 hours of the infant meeting the following criteria

- **$PaCO_2$ < 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.

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 $\pm$ 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.[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 $\pm$ 15 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 $\geq$ 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 $\geq$ 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:***

- $PaCO_2$ < 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 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 Should this be 30 min in view of VON data??) 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.</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 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

Intubation Criteria for non-intubated Control infants > 60 ± 15 (should this be 30 min??) 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 ≥ 88% using study oximeter
- 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 ± 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 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 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.

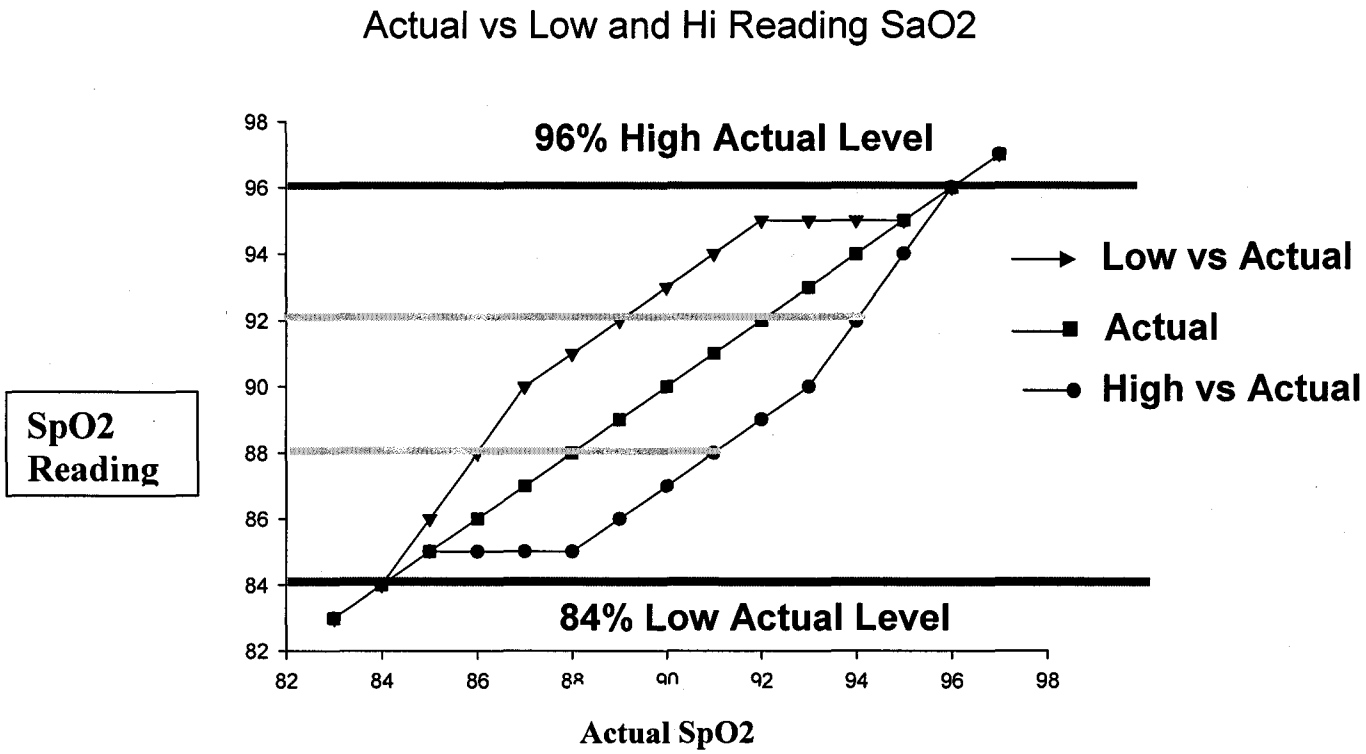
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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.[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

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

		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 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

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,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

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: avroy a fanaroff
To: Higgins, Rosemary (NIH/NICHD)
Subject: Re: Finer Trial
Date: Tuesday, August 19, 2003 9:31:03 AM

Hi
I am involved with senior rounds at that time
I finish at about 11.50 and will try and join if you are still talking
Av
At 12:49 PM 8/15/2003 -0400, you wrote:

> Hi
> Neil would like to have a FU call on Tuesday August 19th at 11 AM EST (8 AM PST). Can you make it?? Let mw know by Mon AM. I believe this is important for finalizing the protocol.
> Thanks
> Rose
>
> Rosemary D. Higgins, M.D.
> Program Scientist for the Neonatal Research Network
> Pregnancy and Perinatology Branch
> Center for Developmental Biology and Perinatal Medicine NICHD, NIH
> 6100 Executive Blvd., Room 4B03B
> MSC 7510
> Bethesda, MD 20892
> (for Fed X use Rockville, MD 20852)
> 301-435-7909
>
> 301-496-3790 (FAX)

From: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: drcpap meeting
Date: Tuesday, August 19, 2003 11:56:52 AM

We can look at giving Finer the suite of the hotel so he can host an early morning meeting.

Carolyn Petrie

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

From:	Petrie, Carolyn
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); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org)
Cc:	Higgins, Rosemary (NIH/NICHD); 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 (UAB) (msumner@peds.uab.edu); 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
Date:	Friday, August 22, 2003 3:00:21 PM
Attachments:	COT ltr to PIs 22Aug03.doc COT study Aug 19 03.doc

---

***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 $\geq$1000 g ($P < 0.02$ and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; $p < .05$, and the proportion of infants ≥1000 g in whom BPD developed decreased from 14% to 9%; $p < .05$. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

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.[293031] 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 ($\leq$ 30 minutes) surfactant and mechanical ventilation.

2) A prospective comparison of a lower (SpO2 range of 85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

Please see **Section 8.2** for further Tables describing details regarding the projected outcomes relative to the study interventions

Randomized Intervention	Low SpO2 85% to 89%	High SpO2 91 to 95%
Early CPAP	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control	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 $\pm$ 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.[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 $\pm$ 15 minutes of age, and if they require > 50% inspired oxygen to maintain their SpO2 $\geq$ 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 $\geq$ 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 $\geq$ 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:***

- $PaCO_2$ < 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 ≥ 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 ± 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 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.

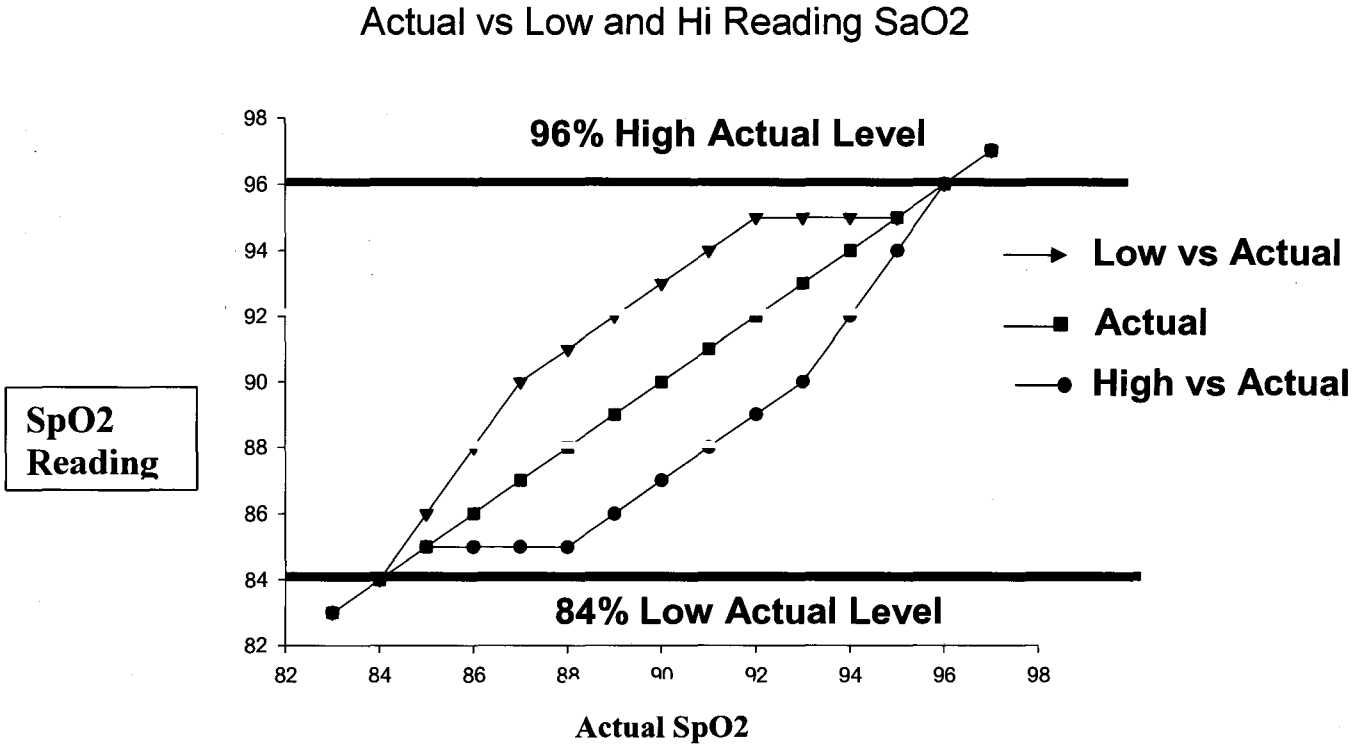
The target oxygen saturation (88-92%) of the CRT output will be the same in both groups (Table).

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: Petrie, Carolyn
To: Higgins, Rosemary (NIH/NICHD)
Subject: RE: COT trial
Date: Friday, August 22, 2003 4:15:15 PM

Rose-
I spoke with Richard about that. He felt strongly about giving them until the 15th (a lot of people gone until September, time to present to the departments and read through the study). Please advise...
Carolyn

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]
Sent: Friday, August 22, 2003 4:11 PM
To: 'Petrie, Carolyn '
Subject: RE: COT trial

Carolyn
I think we wanted all the comments in by Sept. 10.

I found a compuer with internet access.

Rose
-----Original Message-----
From: Petrie, Carolyn
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); M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu); Seetha Shankaran (sshankar@med.wayne.edu); William Oh2 (WOh@wihri.org)
Cc: Higgins, Rosemary (NIH/NICHD); 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 (UAB) (msumner@peds.uab.edu); 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
Sent: 8/22/2003 2:59 PM
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

<<COT ltr to PIs 22Aug03.doc>> <<COT study Aug 19 03.doc>>

From:	Petrie, Carolyn
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)"; "M. D. Waldemar A. Carlo (wcarlo@peds.uab.edu)"; "Seetha Shankaran (sshankar@med.wayne.edu)"; "William Oh2 (WOh@wihri.org)"
Cc:	Higgins, Rosemary (NIH/NICHD); 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)"; Petrie, Carolyn; " (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 (UAB) (msumner@peds.uab.edu)"; "Mazie Tinsley (Emory) (mazie_tinsley@oz.ped.emory.edu)"; " (renee.dunbar-scott@oz.ped.emory.edu)"; Hastings, Betty J.; "Sharon Gonzales (Duke) (gonza025@mc.duke.edu)"; "Wendy Holcomb"; Das, Abhik
Subject:	RE: COT trial
Date:	Monday, August 25, 2003 1:24:42 PM
Attachments:	COT ltr to PIs 22Aug03.doc COT study Aug 19 03.doc

---

UPDATE: Please note that we are moving the deadline to: **Wednesday September 10**

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

From:	Petrie, Carolyn
To:	M. D. Neil Finer (nfiner@ucsd.edu)
Cc:	Higgins, Rosemary (NIH/NICHD); Heidi Squibb (UCSD) (hsquibb@ucsd.edu)
Subject:	COT presentation for centers
Date:	Tuesday, August 26, 2003 3:17:31 PM

Neil-

Do you have a (power point) presentation for all the centers to promote the COT trial?

If so, please send me a copy so I may distribute to everyone.

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:	Richard Ehrenkranz
Cc:	Poole, W. Kenneth; Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer
Subject:	Next Trial COT Trial
Date:	Tuesday, June 17, 2003 12:19:10 AM
Attachments:	Definitive Network Trial June 16.doc

Hi Richard
I tried to phone you today
Please find attached a Protocol for your Committee's review. I know that you were sent one yesterday from Rose. The current version has some important changes regarding the sample size and the management of the study group highlighted in yellow. Our group was of 2 opinions regarding the management of the Control Group. I would ask for input from your committee. I would like this reviewed at the Steering Committee. Sorry for the late notice. We having been revising this almost daily, with help from Ken
Many thanks
See you soon
Neil

Protocol for the NICHD Neonatal Research Network

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

Jan 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))[33]. 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).[34] 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%).[35] 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.[36] 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.[37] 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.[38]

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.[39] 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.[40] 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[4142], 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 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 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.[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 the lowest SaO2 to which they were randomized, (CRT Reading of < 88%), they 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 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, 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 indicated $SaO_2 \geq 88\%$ 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.

CONTROL Group

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 will be intubated in and given surfactant within 30 minutes of birth

OR

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 indicated SaO2 (using the altered Pulse Oximeters) of < 88% will be immediately intubated and given surfactant unless other conditions exist which the clinician believes would be contraindications to surfactant such as pneumothorax.

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 indicated $SaO_2 \geq 88$
- 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.

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. I would ask the Protocols Committee to comment on these 2 alternate approaches.

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.

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 92%, representing a 7% 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 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 89% to 96% representing a 7% 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 %

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.

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.[45][46][47]. 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.

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

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.

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

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

We will select a 10% difference, and use a sample size of 1192 infants < 28 weeks

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 (%)					
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 (%)†					
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 (%)				
PDA requiring surgery				

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] Saugstad. Pediatr Res 53:376A, 2003

[34] 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

[35] 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.

[36] 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

[37] 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

[38] 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

[39] 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

40 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

41 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:	Neil Finer
To:	Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer
Cc:	Higgins, Rosemary (NIH/NICHD)
Subject:	Fw: Surfactant use
Date:	Friday, June 20, 2003 11:35:09 AM
Attachments:	surfact rates.doc

Here is the data for the 26-27 week infants who received surfactant by site which Ken had sent me. The current version of the protocol has both approaches reflecting the current dialogue. We can discuss this at out meeting.
Neil
----- Original Message -----
From: "Poole, W. Kenneth" <poo@rti.org>
To: "'Neil Finer'" <nfiner@ucsd.edu>
Cc: <higginsr@mail.nih.gov>
Sent: Monday, June 16, 2003 11:16 AM
Subject: FW: Surfactant use

Percentage of Infants who Received Surfactant
Infants Born 2001-2002 who were 26 or 27 Weeks Gestational Age
and Survived 12 Hours

Center	Number of Infants Born	Percentage who Received Surfactant
3	74	94.6
4	69	58.0
5	77	89.6
7	7	85.7
8	76	56.6
9	76	82.9
10	3	66.7
11	169	64.5
12	129	89.9
13	53	79.2
14	111	96.4
15	68	100.0
16	133	68.4
18	149	78.5
19	69	79.7
20	121	96.7
21	64	98.4
22	101	91.1
Overall	1549	82.0

From:	Neil Finer
To:	jhouse@ucsd.edu
Cc:	Higgins, Rosemary (NIH/NICHD); Avroy A. Fanaroff, M.D.; Donovan, Edward (DONOVAEF); Shahnaz Duara; Wally Carlo, M.D.; Neil Finer
Subject:	Fw:
Date:	Monday, June 23, 2003 12:18:17 PM
Attachments:	Agenda for Ventilation Committee Meeting June 23.doc

---

Judy
Please print 15 copies of this agenda. I will pick these up this morning at around 10:45
Thanks
Neil
----- Original Message -----
From: Neil Finer
To: hsquibb@ucsd.edu
Sent: Monday, June 23, 2003 8:47 AM

Hello Hiedi
Could you please print out 10 copies of this agenda. I will come in on my way to the airport to pick these up.
Thanks
Neil

Agenda for Ventilation Committee Meeting June 23, 2003

Review current protocol and discuss the following areas:

1. Methodology: Control Patients – Intubate all including 26-27 weeks or use previous version

Control Group – Delivery Room Management : 26 – 27 weeks Strata: Infants will be intubated in and given surfactant within 30 minutes of birth

OR

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 indicated SaO2 (using the altered Pulse Oximeters) of < 88% will be immediately intubated and given surfactant unless other conditions exist which the clinician believes would be contraindications to surfactant such as pneumothorax.

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 indicated $SaO_2 \geq 88$
- 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.

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.

Percentage of Infants who Received Surfactant
Infants Born 2001-2002 who were 26 or 27 Weeks Gestational Age and Survived 12 Hours

Center	Number of Infants Born	Percentage who Received Surfactant
3	74	94.6
4	69	58.0
5	77	89.6
7	7	85.7
8	76	56.6
9	76	82.9
10	3	66.7
11	169	64.5
12	129	89.9
13	53	79.2
14	111	96.4
15	68	100.0
16	133	68.4
18	149	78.5
19	69	79.7
20	121	96.7
21	64	98.4
22	101	91.1
Overall	1549	82.0

2. Discuss Pulse Oximeter settings and ranges Current protocol uses 7% - Do we wan wider range?

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 92%, representing a 7% 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 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 89% to 96% representing a 7% 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.

2. Review Study size estimates and hypotheses:

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

We will select a 10% difference, and use a sample size of 1192 infants < 28 weeks

3. Discuss need for pilot - need to clinically test altered pulse oximeters

4. Discuss budget

5. Discuss current status of DR CPAP Manuscript – Publications committee review.

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, 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:***

- $PaCO_2$ < 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.

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 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).

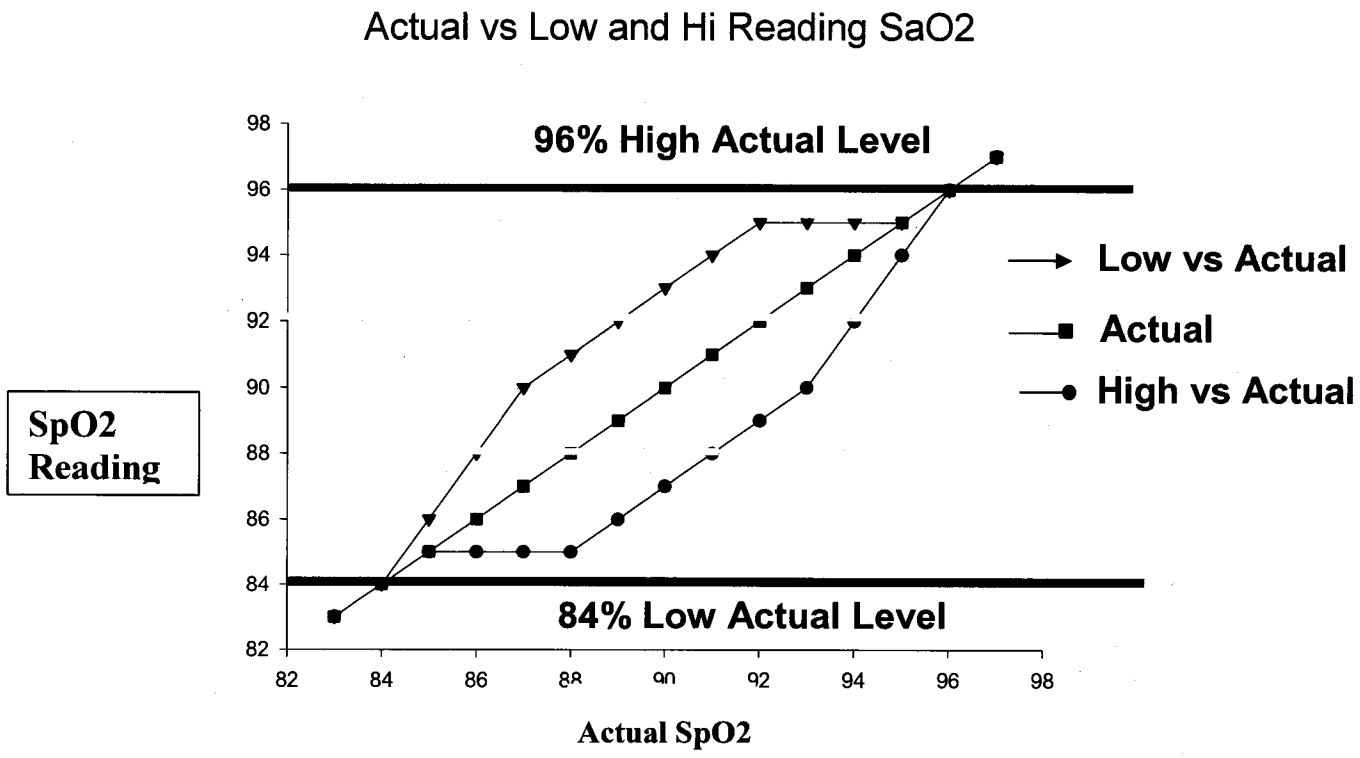
Table. Output and Actual SpO2 Targets and Alarms

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