Protocol for the NICHD Neonatal Research Network

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

The SUPPORT Trial

Final

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1.1 Statement of Problem

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

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

1.2 Background

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

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

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

1.3 Animal Studies

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

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

1.4 Human Experience: Ventilatory Support

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

There is now a body of information from Europe that provides further evidence that early CPAP can reduce the need for intubation in a significant number of VLBW infants. Jonsson et al treated VLBW infants from 1988 to 1993 that required > 30% oxygen with nasal CPAP usually within 30 minutes of delivery[14]. From 1991 onward, infants with severe distress or apnea were intubated for a $PaCO_2$ greater than 60 mmHg, and were given surfactant. Twenty-five percent of all infants required only supplemental oxygen and 24% of all infants were ventilated from birth. Fifty-one percent were treated with nasal CPAP, with one-third of these subsequently requiring ventilation. Almost all infants < 24 weeks required ventilation suggesting that this group may require a different approach. Gittermann et al reported that the use of early CPAP for infants < 1500gm (VLBW) significantly reduced the frequency of intubation, reduced mortality ($p=0.038$), and shortened the duration of intubation and length of stay[15]. In this study the CPAP was applied as soon a signs of respiratory distress occurred (usually within 15 minutes of birth). Poets et al[16] in a report of 2001 VLBW infants (500 to 1499 g) born from 1992 to 1994 reported that there was an increase in the proportion of patients not intubated and mechanically ventilated from 7% to 14% in infants <1000 g and from 28% to 44% in those $\geq$1000 g ($P < 0.02$ and <0.01, respectively). The decrease in intubation was not associated with a significant increase in adverse outcome such as death, intraventricular hemorrhage, periventricular leukomalacia, or BPD. The proportion of infants <1000 g that survived without BPD increased from 38% in 1992 to 48% in 1994; $p < .05$, and the proportion of infants =1000 g in whom BPD developed decreased from 14% to 9%; $p < .05$. None of these observations was from a prospective controlled trial, and in none was there a contemporaneous control group who did not receive early CPAP.

The first prospective trial comparing prophylactic CPAP, started at birth, with conventional management was that of Han et al. They compared the use of nasal CPAP given by nasopharyngeal tube with conventional management in 82 infants, 32 weeks gestational age at birth, and in this study it would appear that CPAP was begun in the DR, but may have been delayed for up to 2 hours.[17] No infants in this trial received surfactant, and no mothers were treated with antenatal steroid. There was no advantage observed with the use of early CPAP, and oxygenation was worse in the early CPAP treated infants. The reviewers of the use of prophylactic CPAP in the Cochrane library concluded that "A multicenter randomized controlled trial comparing prophylactic nasal CPAP with "standard" methods of treatment is needed to clarify its clinical role."[18]

In the post surfactant era, Verder et al conducted the first prospective evaluation of early CPAP (not necessarily delivery room CPAP) and short-term intubation for surfactant administration in a multicenter collaborative trial conducted from September 1991 to October 1992.[19] The primary hypothesis was that the use of early CPAP and brief intubation for surfactant in infants meeting pre-established criteria would reduce the percentage of infants requiring mechanical ventilation from 80% to 40%. Infants randomized to surfactant [Curosurf®] received 200 mg/kg, (2.5 ml/kg) following intubation, with manual ventilation for 2-5 minutes and were then extubated if stable. This study was stopped after an interim analysis demonstrated a significant benefit for the surfactant treated infants. Thirty-three of the 35 infants randomized to early surfactant were extubated after such treatment, and 13 required reintubation at a median of nine hours after surfactant treatment, compared with 28 of 33 control infants who were intubated a median of three hours after randomization, (p=0.003). The overall duration of ventilation in both groups was 2.5 days; there were no other differences between the groups. Verder et al performed a second multicenter prospective trial from April 1995 to January 1997 and enrolled infants <30 weeks with similar criteria to the previous trial, apart from an entry a/A ratio of .35 to .22, which decreased over 30 minutes, which was less stringent, allowing infants to be treated at lesser degrees of oxygen requirement, than their first study. These infants were initially all treated with CPAP and were enrolled up to 72 hours of age (median 4.1 hours, range 0.3 to 40.1hrs).This trial was also stopped after an interim analysis demonstrated a statistically significant reduction in the need for ventilation or death within seven days from 63% in the late-treated infants to 21% in early-treated infants. The median duration of ventilation in both trials was 2.5 days[20]. This study was not a prospective evaluation of early CPAP because CPAP was initiated in all infants at variable ages, and they did not evaluate infants of less than 25 weeks gestation.

Lindner et al recently reviewed their experience using a continuous prolonged (15 seconds duration) pressure controlled (20 to 25 cm H_2O) inflation of the lungs followed by continuous positive airway pressure (CPAP) of 4 to 6 cm H_2O for all ELBW infants immediately after delivery to establish a functional residual capacity (FRC) and to avoid intubation and ventilation[21]. The criteria for subsequent intubation were a $PaCO_2$ > 70 mmHg, an FiO_2 >.6 and respiratory distress with severe recurrent apnea. The rate of early intubation and mechanical ventilation in the delivery room decreased from 84% in 1994 to 40% in 1996. In 1996, 25% of the ELBW infants were never intubated (compared with 7% in 1994). There was no difference in mortality and overall there was less IVH > Grade 2 and BPD for the later cohort. No infant had an air leak upon admission to the NICU, suggesting that use of a prolonged inflation was well tolerated. Only 1 of 11 infants of 24 weeks gestation was able to avoid intubation in this study. Once again, there was no contemporaneous control group who did not receive delivery room CPAP. All of the above studies required high levels of $PaCO_2$ before initiating ventilation for this indication.

There is retrospective evidence suggesting a benefit for early CPAP in experiences from the USA. A survey of eight neonatology units in the USA in 1987 demonstrated that one unit, Columbia, had the lowest rate of CLD[22]. A more recent comparison of practices and outcomes between two neonatology units in Boston and the Babies and Children's Hospital unit (Columbia) evaluated VLBW infants born in 1991 to 1993.[23] This study revealed that 75% of infants at the Boston centers were initially treated with mechanical ventilation compared with 29% at Columbia, whereas initial CPAP was used in 63% of infants at Columbia vs. 11% at the Boston centers. Columbia also used less surfactant, 10% versus 45%, (all $p<0.001$). In addition the rates of CLD were significantly lower at Columbia compared to the other two centers (4% vs. 22%).

de Klerk and de Klerk recently published a five-year retrospective review of the outcome of 1 to 1.5 kg infants (n-116) treated with early CPAP vs. usual care (delayed CPAP)[24]. During 1996 -1998 infants were placed on CPAP within 10 minutes of admission (they did not describe the use of delivery room CPAP). Early CPAP beginning following admission to the neonatal unit decreased endotracheal intubation from 65 to 14%, $p<0.001$ and surfactant use (40 to 12%, $p<0.001$). Ventilator days were reduced from a median of 6 to 2 days ($p<0.01$) and oxygen supplementation or death at 28 days from 16 to 3%, $p<0.05$. Oxygen supplementation or death at 36 weeks did not significantly decrease (11 to 3% $p=0.25$). Ventilation and surfactant use were very high during the delayed CPAP (control period) so it is unclear whether other improvements in care may have coincided with the change to early CPAP.

Sandri et al[25] have recently published preliminary data from a multicenter randomized controlled trial of 155 infants 28 to 31 weeks gestation randomized to CPAP within 30 minutes of birth or to CPAP if the FiO_2 requirement exceeded 40%. Use of surfactant (22 to 21%, NS) and ventilator support (10 to 9%, NS) was not reduced with early CPAP. However, this trial included relatively bigger infants and the control group received CPAP at relatively low FiO_2, minimizing the difference between the experimental and control groups. This study did not evaluate the use of delivery room CPAP.

More recently Thomson et al presented the results of a multicenter trial of 237 infants from 27 to 29 weeks gestation[26], who were randomized to prophylactic surfactant followed by nasal CPAP using the Infant Flow DriverTM, early nasal CPAP followed by rescue surfactant, early IPPV with prophylactic surfactant, and conventional management. They reported that CPAP was initiated by 6 hours of age in 76% and 79% of the first 2 treatment groups, and those infants in the CPAP and rescue surfactant and prophylactic surfactant followed by CPAP groups required the lowest duration of ventilation. There were no differences in the incidence of CLD or other neonatal complications. Neither of these studies instituted the use of CPAP in the delivery room.

In a preliminary feasibility trial we have evaluated the ability of 5 sites of the NICHD Network to initiate CPAP during resuscitation, and continue its use in the NICU. In that study 103 infants were randomized to receive resuscitation with either CPAP/PEEP or no CPAP/PEEP. All infants were treated with CPAP following NICU admission. During delivery room resuscitation, 46 infants were intubated, 27 of 55 CPAP infants and 19 of 48 control infants ($p=0.33$). All 23 week gestation infants were intubated in the delivery room, irrespective of treatment group, whereas only 3 of 22 (13%) infants of 27 weeks required such intubation. When evaluated by birth weight, all 3 infants of less than 500 gm birth weight and 6 of 11 infants between 500-600 gm birth weights were intubated in the delivery room. All remaining infants were admitted to the NICU and had CPAP initiated. For infants not intubated in the DR, 36 infants were subsequently intubated in the NICU by day 7, 16 CPAP infants and 20 Control infants, ($p=0.21$). Infants in the CPAP group developed criteria for intubation sooner than the Control infants, with means and medians of 10.5 and 1.8 hours versus 20.7 and 3.3 hours,

p=0.41. These infants met criteria established for this trial which included an FiO2 > .3 to maintain an SpO2 > 90% or a PaO2 > 45 torr, an arterial PaCO2 > 55-60 with a pH < 7.25. or apnea requiring bag and mask ventilation. CPAP infants were intubated at an average FiO2 = 0.5 compared to 0.4 for control infants.

The literature thus suggests that early CPAP may be of substantial benefit, although none of this information has been obtained from prospective randomized trials of CPAP randomly applied in the delivery room to a population of VLBW or ELBW infants, with an appropriate control group. The terms early CPAP in the above studies (apart from that of Lindner et al[15]) involved the application of CPAP shortly following birth, not immediately after delivery. It is not surprising, therefore, that the recent revised NRP guidelines do not mention the use of CPAP/PEEP for neonatal resuscitation.[27] There is also some evidence that the level of CPAP needed may vary depending on the actual device utilized. Pandit et al and Courtney et al have demonstrated that variable flow CPAP was associated with a lower work of breathing and increased compliance at all levels of CPAP whereas constant flow nasal CPAP increased compliance only at 8 cm H2O.[28] In addition, variable flow CPAP devices were effective at recruiting lung volume at all tested CPAP levels.[29] A more recent trial compared the use of variable flow CPAP to conventional CPAP at extubation for 162 ELBW infants and reported no significant differences with either form of CPAP.[30] This study noted that 40% of ELBW infants failed extubation primarily because of apnea.

There are no studies in the surfactant and antenatal steroid era which have prospectively compared delivery room, CPAP with a more conventional approach, such as the use of prophylactic surfactant and conventional ventilation. The current available evidence demonstrates that prophylactic natural surfactant treatment significantly decreases mortality, air leak, and BPD in preterm infants.[31] Early surfactant, defined as surfactant at less than 2 hours of life is also of benefit and reduces air leaks, and mortality.[32] These reviewers noted that “early surfactant administration significantly reduces the risk of key clinical outcomes including pneumothorax, PIE, chronic lung disease, and neonatal mortality. Given the efficacy of prophylactic surfactant therapy (Soll 1999), this meta-analysis suggests that early selective surfactant administration to intubated infants with early signs of RDS may be part of a clinical spectrum of improved outcomes with earlier treatment”. The most recent experience regarding early surfactant was presented by Horbar et al at the SPR in May, 2003. Their study which involved a cluster randomization in 57 NICUs of a practice to administer surfactant earlier compared with 57 control NICUs. They noted that infants at the intervention sites received their surfactant more often in the DR (54.7 vs 18.2%, p < 0.001) and earlier than the control sites (21 vs 78 minutes, p <0.001). There were no differences in mortality and pneumothoraces, the intervention centers had a lower rate of overall and severe IVH (28% vs 33%, p < 0.04, 10% vs 14%, p < 0.001) which were secondary outcomes of this trial. [33]

The most recent published study by Tooley and Dyke evaluated the use of prophylactic surfactant and early extubation to CPAP versus prophylactic surfactant and continuing management.[34] In this study 42 infants of 25 to 28(+6) wk of gestation were intubated at birth and given one dose of surfactant. They were then randomized within one hour of birth to either continue with conventional ventilation or to be extubated to nCPAP. They reported that 8 out of 21 (38%) babies randomized to nCPAP did not require subsequent re-ventilation. (Ventilation rates of 62% vs 100%, p = 0.0034). The smallest baby successfully extubated weighed 745 g. There were also significantly fewer infants intubated in the nCPAP group at 72 h of age (47% vs 81%, p = 0.025). There was no significant difference between the two groups in the number of babies that died, developed chronic lung disease or severe intraventricular hemorrhage. This study demonstrates that a significant number of very preterm babies with RDS can be extubated

to nCPAP after receiving one dose of surfactant. The current SUPPORT study will address this population, extended to 24 weeks, using a similar methodology for the infants of 24 to 27 6/7ths weeks who fail initial CPAP, with adequate power to determine if this approach is associated with significant benefits in terms of important short and longer term clinical outcomes.

Oxygen Saturation:

There is now an emerging body of information that suggests that many of the morbid conditions associated with extreme immaturity are potentiated by an excess of free-radicals occurring in infants who are intrinsically deficient in antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase. During hypoxia, metabolic alterations prime hypoxic cells to produce free oxygen radicals when subsequently exposed to oxygen. Such reperfusion injury, in addition to increasing the production of free oxygen radicals, is associated with other metabolic changes which may produce long lasting harmful effects. Silvers et al reported that a low plasma antioxidant activity at birth in premature infants was an independent risk factor for mortality.[35] Pulmonary oxygen toxicity, through the generation of reactive oxygen/nitrogen species in excess-of antioxidant defenses, is believed to be a major contributor to the development of BPD.[363738] For example the preterm macrophage showed a significant increase in cytokine mRNA and protein after overnight incubation in 95% oxygen compared with cells from term animals. Only macrophages from premature animals had a significant increase in intracellular oxygen radical content, measured by 2', 7'-dichlorofluorescin analysis, after incubation in 95% oxygen. This enhanced inflammatory cytokine response to oxygen has been postulated to be a mechanism involved in the early development of chronic lung disease in premature infants.[39] Varsila et al noted that immaturity is the most important factor explaining free radical-mediated pulmonary protein oxidation in premature newborn infants and that oxidation of proteins is related to the development of chronic lung disease.[40]

There are a number of prospective randomized trials that have compared the use of room air with 100% oxygen for neonatal resuscitation, and these have reported Infants resuscitated with room air resumed spontaneous breathing faster and required less positive pressure ventilation than infants resuscitated with oxygen.[41 42] Vento et al also demonstrated that that infants resuscitated with oxygen demonstrated long lasting evidence of oxidative stress and activities of superoxide dismutase and catalase in erythrocytes that were 69% and 78% higher, respectively compared with control infants resuscitated with room air at 28 days of postnatal life.[43] A recent meta-analysis of room air vs 100% oxygen resuscitation comprising of 1,693 infants in five trials revealed decreased neonatal resuscitation in infants resuscitated with room air (6 vs 11%, $p<0.005$ or 0.57 (95% CI 0.40 – 0.81))[44]. While these studies described results of mostly term infants, some infants were premature and the premature infant is known to have decreased antioxidants which would increase their susceptibility to oxygen toxicity. In the only randomized prospective trial to evaluate room air compared with oxygen in preterm infants, Lundstrom et al resuscitated infants of less than 33 weeks gestation who were randomized to receive either 80% oxygen or room air and noted that 2 hours following delivery, the room air infants had a higher cerebral blood flow compared with oxygen resuscitated infants. (median (interquartile range)): 15.9 (13.6-21.9) v 12.2 (10.7-13.8) ml/100 g/minute).[45] They did not find any significant differences in short or long-term outcomes but did note that SpO2 was lower in the room air infants with values at 5 and 7 minutes of 75% and 80% compared with 92% and 94% in the 80% oxygen group ($p<0.001$). Current monitoring with pulse oximetry using limits of 95 to 96% will result in significant periods wherein the infants actual PaO2 may increase to very high levels, as there are rapid increases in PaO2 with very small increments in SpO2 at this plateau portion of the hemoglobin dissociation curve.

Tin et al retrospectively reviewed outcomes for infants admitted to various neonatal intensive care units in northern England from 1990 to 1994 and managed with lower (70-90%) or higher SpO2 ranges (88%-98%).[46] They reported that infants who were managed for at least the first 8 weeks of life with SpO2s from 88-98% developed retinopathy of prematurity severe enough to be treated with cryotherapy four times as often as infants managed with the lower SpO2 ranges. Infants managed with the lower SpO2 ranges did not have increased risk of mortality or neurodevelopmental impairment. Bancalari et al using transcutaneous oxygen monitoring were able to show that infants who received continuous monitoring had a similar incidence of ROP to infants who were monitored by intermittent sampling had similar incidences of ROP, however for subgroup of infants $\geq$ 1100gm, there was a decrease in the incidence of ROP.[47] The STOP-ROP trial randomized infants with already established pre-threshold retinopathy and an SpO2 less than 94% to two ranges of SpO2 (89% to 94% versus 96% to 99%), for at least 2 weeks and until both eyes were at study endpoints. The higher range of SpO2 was associated with a non-significant decrease in the progression of ROP, but was associated with a greater need for oxygen and more exacerbations of BPD.[48]

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

The most recent trial conducted in Australia compared SpO2 ranges of 91% - 94% versus 95% - 98% in 358 infants of less than 30 weeks who remained oxygen dependent at 32 weeks. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months. The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days; P<0.001) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy. but resulted in an increased duration of oxygen supplementation.[50] They reported that additional oxygen supplementation did not improve survival, growth, or the occurrence of cerebral palsy at 18 to 24 months. Anderson et al have recently reported the results of a survey of pulse oximetry practices in 142 NICUs in the USA and noted a wide range of monitoring limits from 82% to 100%. They reported a lowered rate of ablative eye surgery in units that used lower maximal SpO2 limits, with the lowest range seen in units that had a maximum SpO2 of < 92%.[51]

In a recent review of oxygen toxicity in the premature infant Weinberger et al recommended that a strategy of limiting oxygen supplementation should be explored to reduce significant morbidities in the premature infant.[52] No studies to date have prospectively randomized ELBW infants to differing oxygenation ranges from birth onwards to determine if there is a benefit of lower versus higher saturation ranges.

1.5 Recent Relevant Studies

We have recently evaluated an FDA approved device specifically designed to facilitate neonatal resuscitation (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand). This device has a t-piece that attaches to a mask and to a simple pressure generator. The inspiratory pressure can be set to a determined level, and a twist valve at the top of the t-piece determines the end-expiratory pressure. Most operators, with the exception of experienced respiratory therapists cannot routinely deliver a predetermined level of positive inspiratory pressures and PEEP[53] using an anesthesia-type manual bag and a neonatal manikin. In contrast, all operators could deliver the predetermined pressures with little intra-individual variation using the Neopuff®. The device operates identically using either a mask or endotracheal tube connection with or without PEEP/CPAP and the operator can adjust the positive inspiratory pressure (PIP) manually during resuscitation. At a flow of 10 liter per minute (lpm) or less, the maximum inadvertent CPAP/PEEP is 0.5 cm H_2O; which does not increase up to rates of 80 breaths per minute, the highest tested rate. The wave form is square, and is more similar to ventilator wave forms than to wave forms obtained using an anesthesia device. It should be noted, that the standard anesthesia devices used in delivery rooms may not deliver the desired CPAP/PEEP, depending on the operator's experience and skill, and may result in overshooting the desired PIP, even when the device is used by experienced operators. The Neopuff® device is now used as the standard resuscitation device in a number of hospitals in the USA, including at least two units in the NICHD Network.

There has been a recent trial evaluating earlier criteria for retinal laser ablative surgery for ROP, the ETROP study.[54] This study has demonstrated that using such criteria the visual outcomes are improved and reported that grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01)and that unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. They recommend retinal ablative therapy for eyes with type I ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. While these results are likely to be integrated into Network practice, there is currently no baseline data regarding the number of infants who would meet these criteria, and thus we will utilize the presence of Stage 3 or greater ROP and/or the receipt of retinal surgery to power our current trial.

2.1 Study Design

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

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ($\underline{<}$ 1 hour) surfactant and mechanical ventilation.

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

or oxygen.

The oxygen saturation monitoring portion of our study will be designed to parallel the planned POST-ROP trial, a multicenter, multinational prospective trial to evaluate different SpO2 levels from birth.[55] The methodology described under oxygen monitoring (**Section 4.1B**) was developed for the current protocol to allow a blinded comparison of 2 different SpO2 levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial, and the POST-ROP study group has agreed to use the ranges described in this protocol, and the methodology that will allow the oximeters to provide actual SpO2 values when the SpO2 is < 85% and > 95%(Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO2 values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

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

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Treatment **Early CPAP**	Early CPAP + Low SpO2	Early CPAP + High SpO2
Control **Prophylactic/Early Surfactant**	Control + Low SpO2	Control + High SpO2

2.2 Primary Hypotheses

1). We hypothesize that relative to infants managed with prophylactic/early surfactant and conventional ventilation that the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). We hypothesize that that relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

2.3 Secondary Hypotheses

We hypothesize that the use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.

- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

3.1 Study Population

Study subjects are infants of 24 0/7ths to 27 6/7th weeks at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) will be enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. It is important to note that previous studies have included few, if any infants less than 25 weeks gestation and such infants are not included in the current COIN trial or the proposed Vermont Oxford Trial. Such infants will be enrolled in this trial because they are the group of infants with the highest mortality and morbidity. The feasibility trial demonstrated that the 5 NICHD centers involved could reduce intubation in the delivery room to less than 50% of such infants if they are not intubated for surfactant. We will exclude infants of 23 weeks or less in view of their extremely high mortality and morbidity, and their almost universal need for delivery room intubation for resuscitation. We have included Tables at the end of the protocol utilizing infants from 23 to 28 weeks to demonstrate that our sample size estimates will not be adversely affected if we should choose to include infants of 23 and/or 28 weeks.

Strata: There will be 2 randomization strata, infants of 24 0/7ths to 25 6/7ths weeks, and infants of 26 0/7ths-27 6/7ths weeks by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study will not be powered to detect outcome differences between strata.

3.2 Inclusion Criteria

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

3.3 Exclusion Criteria

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

3.4 Sampling Recruitment and Screening Procedures

Infants will be recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

3.5 Screening Procedures

All admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. We will inform our obstetrical colleagues at each involved institution of the nature of this study, and encourage them to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery

3.6 Other Procedures

A T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology will be used at all sites for the delivery room administration of CPAP. A training video to explain the proper use of the Neopuff® will be provided to any site which wishes to use it and is not familiar with the device.

3.7 Randomization

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

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

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

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

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

3.8 Informed Consent:

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

3.9 Management and Retention of Study Population

All enrolled infants will be seen at follow-up-up at 18 to 22 months corrected age. We do not anticipate a significant loss other than death (13% in the first 12 hours , approximately 32% before discharge, based on year 2000 registry data), and will plan for a further 15% attrition.

4.1 A: Study Intervention: Mode of Ventilatory Support

The intervention will begin after birth when the infant is given to the resuscitation team. The conduct of the resuscitation will follow usual guidelines, and once stabilized, all Control infants in both strata will receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants will be placed on CPAP/PEEP following stabilization, and be intubated only for resuscitation indications.

The assignment to either a high or low SpO2 by study oximeter assignment will be performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission.

TREATMENT: CPAP Group : Early Extubation and CPAP

Delivery Room Management

FiO2:

Standard of care.

CPAP:

CPAP or ventilation with PEEP will be utilized if the infant requires positive pressure during resuscitation. CPAP will be continued until admission to the NICU using the Neopuff or equivalent device and a face mask or nasal prongs. Initial PPV will be at a PIP of 15-25 cm H_2O and a PEEP/CPAP of 5 cm cmH_2O.

Intubation:

Infants may not be intubated for surfactant only in the DR. Infants who require intubation for resuscitation will receive surfactant within 60 minutes of birth.

Intubation will be performed only for the standard NRP indications including failure to respond to PPV with evidence of continuing cyanosis or bradycardia, the need for chest compressions, the need to administer intratracheal medications, or other situations in which the resuscitation team determines that surfactant is urgently required.

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

The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management

These infants will be managed on nasal CPAP, and intubation is never required by protocol. They *MAY* be intubated if they meet ***ANY*** *of* the criteria listed below. If intubated within the first 48 hours of life they should receive surfactant

Intubation:

- An FiO_2 >.50 required to maintain an indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour
- An arterial $PaCO_2$ > 65 torr (arterial or capillary samples, if venous PvCO2 > 70 torr) documented on a single blood gas within 1 hour of intubation
- Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. (Note that clinically defined shock is an accepted indication for intubation.)

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

These criteria will continue in effect for a minimum of 14 days of life.

Intubation performed without meeting any of the above criteria will be considered a study protocol violation unless extenuating circumstances are noted.
(e.g. - Upper airway obstruction (choanal atresia, micrognathia/glossoptosis)).

Extubation:

An intubated CPAP-Treatment infant ***MUST*** *have extubation attempted within 24 hours if* **ALL** *of the following criteria are met and documented on a single blood gas*

- $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples)
- An indicated SpO2 $\leq$ 88% with an FiO2 $\leq$ 50%
- A mean airway pressure (MAP) < 10 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFV)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic/vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA

These criteria will continue in effect for the first 14 days of life.

Failure to extubate an infant meeting all of the above criteria will be recorded as a study protocol violation unless extenuating circumstances are noted. (e.g. - PIE, air leak)

Reintubation

If a Treatment infant is extubated as per Protocol Criteria, and requires re-intubation for any indication, any further attempt at extubation may be delayed for 24 – 48 hrs based on the clinician's decision.

Re-intubation criteria are the same as those for Intubation for the CPAP infants. Thus, intubation is not required, but these infants **MAY** be reintubated if they meet **ANY** of the following:

Re-Intubation Criteria:

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

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

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

D/C CPAP

Treated infants who remain in Room Air for at least 1 hour may have their CPAP discontinued. CPAP may be discontinued earlier and follow unit Standard of Care. CPAP may be restarted at any time in such infants.

CPAP infants who require intubation three times, for any criteria, will have all subsequent treatment including subsequent extubations and any further re-intubations performed using unit Standard of Care. This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

Surfactant

Infants intubated in the first 48 hours for respiratory distress should be given a minimum of one dose of surfactant

Up to 4 surfactant administrations may be given if the FiO2 is greater than 50% following manufacturers' recommendations for dose and dosing interval.

Explanation:

The purpose of the above criteria is to minimize the duration of intubation of Treatment infants. The Criteria for extubation are more severe than those of the Control Group infants, and extubation must be attempted for any infant who fulfills the stated criteria.

The criteria for re-intubation recognize that intubation is traumatic, and is designed to avoid frequent attempts at extubation for infants who fail.

CONTROL- Prophylactic/Early Surfactant and Ventilation

Delivery Room Management:

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 min minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current center practice.

NICU Management:

:

***Extubation*:**

An intubated Surfactant-Control infant will continue to receive mechanical ventilation until extubation criteria are satisfied, but **MUST** have Extubation attempted within 24 hours of fulfilling ***ALL*** of the following criteria documented on a single blood gas.

- $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples)
- An FiO2 = 35 with a SpO2 = 88% using the study pulse oximeters with
- A mean airway pressure (MAP) < 8 cm H_2O, ventilator rate $\leq$ 20 bpm, an amplitude < 2X MAP if on high frequency ventilation (HFO)
- Hemodynamically stable (Defined as an infant with clinically acceptable blood pressure and perfusion in the opinion of the clinical team – such an infant may be receiving ionotropic / vasopressor agents, but should not require ongoing volume infusions to stabilize the circulation and the doses of any continuously infused medications for circulatory stabilization should not have increased within 1 hour of any planned extubation).
- Absence of clinically significant PDA (Defined as bounding pulses, audible murmur and Echo confirmation of L-R shunting with increased LA/Ao size

These criteria will continue in effect for a minimum of 14 days for all infants.

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

Weaning

This protocol will not define strict weaning criteria for the Control infants, but it is to be understood that reasonable attempts should be made to extubate these infants. While it is understood that some centers may be using somewhat more severe FiO2 and PaCO2 criteria than those listed here as current practice, these Criteria are thought to reflect current Network practice and practice at 2 of the 3 Best practice centers.

Reintubation:

- Control Infants may be reintubated using Standard of Care.

Explanation:

Control infants are to be treated using an approach considered similar to current standards of care. Apparatus for resuscitation for Control Infants at each center will represent their usual equipment for the resuscitation of an ELBW infant. The Neopuff may be utilized for such infants as above, but this is not mandatory. It is anticipated that the majority of these infants will be intubated and receive surfactant in the delivery room.

4.1 B: Study Intervention: Low versus High SpO2 Range:

There will be 2 ranges of SpO2 utilized during this trial. The Low target range will be 85% to 89% and the High target range will be 91% to 95%. The altered Pulse Oximeters (PO) are described below, and will display a range of 88% to 92% when the SpO2 ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO2 is approximately 86%, and 92% when the actual SpO2 is 89%. Similarly the High range PO will display 88% when the actual SpO2 is 91% and indicate 92% when the actual SpO2 is approximately 95%. See below for further explanation. This deviation is similar to the BOOST trial which used a continuous 3% offset.[42] As an added safety feature, the POs used in this trial will revert to the actual SpO2 values and allow the caretakers to be aware of actual SpO2 values < 85% and > 95%.

Low Range Infants:

These infants will be monitored with a target SpO2 range of 85% -89% with suggested indicated alarm limits of 85% and 95%, representing approximately a 10% span for alarms as long as the infants are receiving any ventilatory support, CPAP, and/or supplemental oxygen. **The study pulse oximeters will be applied to the infant within two hours following NICU admission.** The assigned PO will remain on the infant and will be removed once the infant has been in room air and off ventilatory support or CPAP for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

High Range Infants:

These infants will be monitored with a target SpO2 range of 91% -95% with suggested indicated alarm limits of 85% to 95% representing approximately 10% span for alarms as long as they are receiving any ventilatory support, CPAP and/or supplemental oxygen. The study pulse oximeters will be removed once the infant has been in room air for 72 hours, and if oxygen is subsequently required a similar altered pulse oximeter providing the same SpO2 range will be used until 36 weeks PCA.

These interventions will be delivered using specially developed pulse oximeters whose displays (the actual readings seen by caretakers) will be adjusted so that the randomized range of SpO2 (either 85%-89%, or 91%-95%) will be indicated by a range of 88%-92%. This is done by progressively altering the offset as the alarm limits are approached, and Masimo has confirmed that this technology is workable. The target oxygen saturation (88-92%) of the display will be the same in both groups as indicated in Table1 below.

These POs will be able to display trend plots of the SpO2 display for a preceding interval to allow the caretakers to receive feedback regarding the actual SpO2 ranges of their baby.

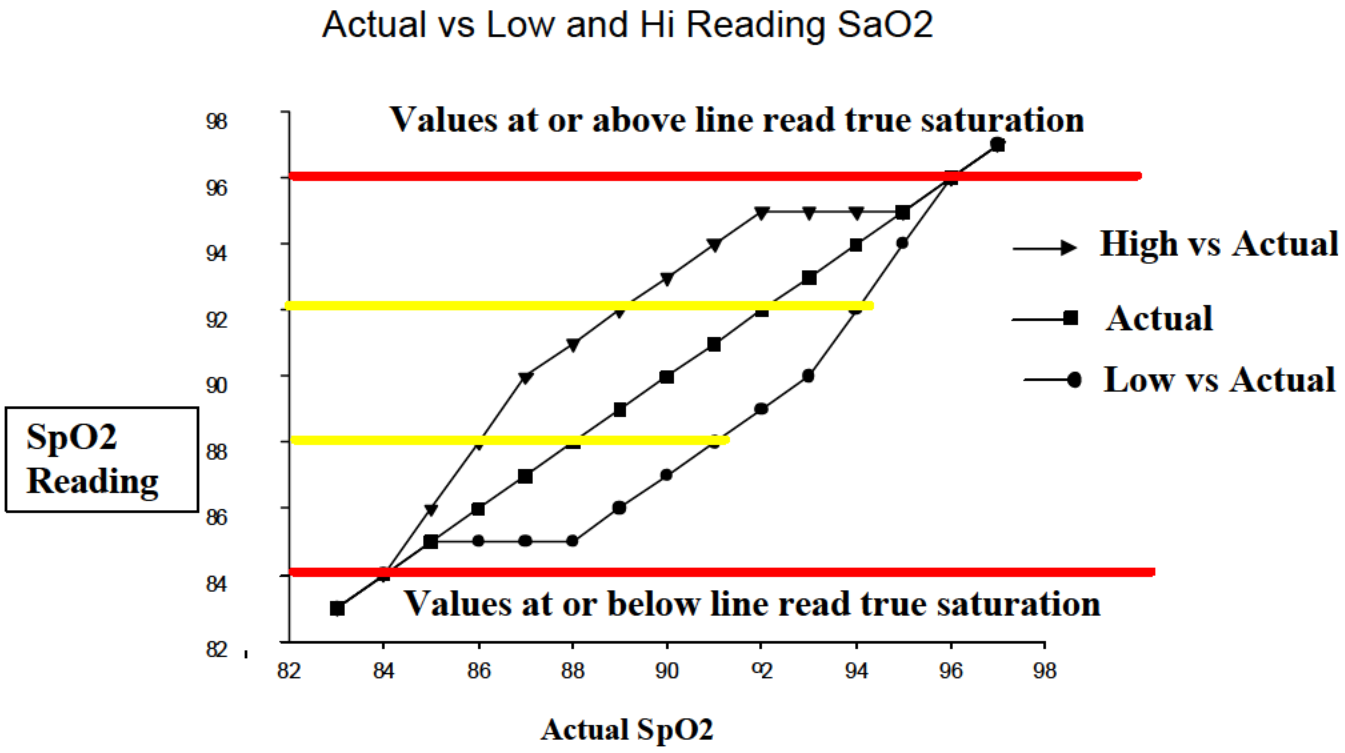
The suggested alarms limits will be 84% and 96% for both groups.

Table 1. Output and Actual SpO2 Targets and Alarms

SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

The pulse oximeters will display the actual reading when then the SpO2 is below 85% and above 95%. This will provide for an overall set of limits on actual SpO2 of 84% to 96% which we believe will avoid unacceptable levels of hypoxia, (< 85%) and hyperoxia (> 95%) **All data below 85% and above 95% will be unaltered on all oximeters**. An averaging time of 16 seconds will be applied in keeping with the settings used by POST-ROP. The preset alarm delay will be 10 seconds. The fail-safe alarm will alarm whenever the reading is 5% below the low alarm limit, in the study this will be at 80%. Some network centers use an averaging interval of 30 seconds, others use very short averaging times. This setting will allow for appropriate response times without unmasking the caretakers.

We believe that this methodology will provide an acceptable ethical design for this trial. The diagram below demonstrates how the pulse oximeter readings are altered between values of 85% to 95%. Readings below or above these levels will not be altered, and will represent actual SpO2 as determined by the pulse oximeter. Note that the entire range of actual SpO2 is altered to either a lower (Low SpO2 Group) value or higher value (High SpO2 Group) till the ends of the alarm ranges of 85% and 95% which will ensure that the infants SpO2 will be separated throughout this range.



Every 30 days until 36 weeks PCA or until the infant is no longer receiving ventilatory support or oxygen, the stored actual SpO2 values (one value per 10 seconds of monitoring) will be downloaded and transmitted to RTI for subsequent analyses. (This interval of sampling may change to a less frequent interval for the convenience of the study personnel, without losing significant data). These data points will be used to confirm that the infants were managed at the

target ranges and provide objective confirmation of the SpO2 Group assignments. The technology for downloading and interpreting this data was used in the DR CPAP Pilot trial, but recent technology utilizing a software program (Profox, Profox Inc, Escondido, Ca) which has been written to facilitate this process, will dramatically simplify this procedure.

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

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

4.2 Delivery of Interventions

CPAP/PEEP in the DR

CPAP and positive pressure ventilation (PPV) in the delivery room for Treatment infants will be administered via a T-piece resuscitator, a neonatal ventilator or an equivalent device that is currently used by the site for the delivery of CPAP. (See **3.6**).

Use of Nasal SIMV;

This approach is currently used by some Network units and has been previously established as being superior to CPAP following extubation in three prospective trials.[56,57,58] For uniformity nasal SIMV may be used in place of CPAP ***only following extubation for both Treatment and Control infants.***

Use of Caffeine:

Caffeine may be administered 2 hours prior to planned extubation, and for any clinically significant apnea.[59]

Surfactant Type:

All centers are asked to follow current unit practice in determining the type of surfactant utilized, and manufacturers' recommendations for redosing intervals.

The protocol requires that at least one dose of surfactant be administered to any infant intubated within 48 hours of birth, with evidence of respiratory distress, who has not previously received surfactant.:

Postnatal Steroids

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

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

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

Head Ultrasound

If a Head ultrasound is done between days 4 and 21 the results will be recorded for this study. If one is not done for standard of care, the study requires that at least one HUS be completed during this window

4.3 Protocol Violations:

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

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

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

4.4 Adverse Events

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

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

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

4.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. Obrien-Fleming [61] boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock [62] boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.

5.1 Measurement Methods:

The PO stored data will be retrieved using a routine provided to all site coordinators, and the resultant data file will be sent electronically to RTI to be included as part of the study data collection.

5.2 Schedule of Data Collection: (See Data tables in Appendix A)

5.3 Primary and Secondary Outcome Measures

5.3.1 Primary Outcome Measure

The primary outcome will be the percentage of infants surviving without BPD (using the Physiologic Definition) or severe ROP (threshold disease or the need for surgery).

5.3.2 Secondary Outcome Measures

- The five minute Apgar score
- The percentage of infants with death or neurodevelopmental impairment at 18 months
- The total duration of mechanical ventilation during the entire NICU stay
- The percent of infants alive and off ventilation by day 7
- The proportion of infants receiving surfactant treatment
- The incidence of air leaks on admission and overall
- The incidence of BPD at 36 weeks using the physiologic definition of BPD
- The incidence of death
- The proportion of infants with severe IVH
- The proportion of infants with PVL
- The proportion of infants with threshold ROP and requiring surgery for ROP
- The proportion of infants requiring endotracheal intubation before 10 minutes of age
- The proportion of infants with of air leaks on admission and overall
- The duration of oxygen supplementation
- The percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- The proportion of infants who receive postnatal steroids to prevent or treat BPD
- The proportion of infants with who develop necrotizing enterocolitis (NEC)
- The proportion of infants with cerebral palsy at 18-22 month follow-up

6.1 Training Study Personnel

6.1.1 Job Descriptions of Study Personnel

The NICHD coordinators will assist the respiratory therapists in each unit regarding the set up the equipment for the delivery of CPAP in the delivery room, and in the NICU.

6.1.2 Training of Personnel

There will be a training session held in Cincinnati about the delivery of CPAP in the delivery room and in the NICU, and a review of available devices that may be used for this intervention.

7.1 Data Collection and Management

We will develop the required CRFs as per Network procedures. It will be our aim to minimize these to ensure that data is collected regarding the intervention, the adherence to the protocol for intubation, surfactant administration, and extubation, and the occurrence of the primary and secondary end-points. All remaining information will be extracted for the current data forms.

8.1 Statistical Analysis

8.1.1 Analysis Plan

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

8.2 Sample Size

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

Subgroup	Death/BPD	Death/> Stage III ROP	Death/NDI
23-27 GA	70.6	53.1	65.7
24-28 GA	64.8	44.5	59.3
24-27 GA	66.6	46.8	60.7
23-28 GA	68.6	50.4	64.0

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

50% for all subgroups (i.e. ranges from 49.7% to 50.0%). Hence one sample size table suffices for all.

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

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

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

TOTAL SAMPLE SIZES REQUIRED

	80% Power		90% Power	
Detectable Difference (absolute %)	Total N1*	Total N2**	Total N1*	Total N2**
8%	1792	2096	2284	2676
9%	1388	1624	1792	2096
10% (multiples to same arm)	1120	1312	1456	1704
11%	940	1104	1208	1416
12%	784	920	1032	1208
13%	672	788	860	1008
14%	584	680	756	880
15%	504	588	652	768

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

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

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

HYPOTHESIZED TREATMENT EFFECTS FOR SUPPORT

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

--BPD/Mortality—67%
--ROP $\geq$ Grade III/Mortality—47%
--NDI/Mortality—61%.

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

Table IA

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

SpO2

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

Table IB

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

SpO2

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

Table IIA

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

SpO2

SpO2

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

Table IIB

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

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

Table III

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

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

9.1 Quality Control

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

10.1 Risks and Benefits

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

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

Appendix A

Study Tables

Table 1. Patient Description

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

Table 2. Other Outcomes

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

Appendix B

Study Tables

Table 1. Patient Description

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

Table 2. Primary Outcomes

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

Table 3. Secondary Outcomes

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

†Analyzed for survivors

Table 4. Other Outcomes

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

	Early CPAP/Early Extubation	Prophylactic Surfactant
Delivery Room Management	Resuscitate using CPAP. If necessary, initial PPV settings PIP 15-25, PEEP 5. Transport on CPAP If intubated for resuscitation, give surfactant within 1 hour of age. Do not intubate unless indicated by NRP guidelines	Intubate and give surfactant within 1 hour of age Transport with PPV according to SOC
Upon NICU Admission	Randomize within 2 hours to Pulse Oximeter	Randomize within 2 hours to Pulse Oximeter
Intubation Criteria	**Not Required. May intubate for ANY of these criteria** • FiO_2 >.50 required to maintain indicated SpO2 $\geq$ 88% (using the altered Pulse Oximeters) for one hour • $PaCO_2$ > 65 torr (art. or cap. samples, if venous $PaCO_2$ > 70 torr) documented on a single blood gas • Hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support for a period of 4 hours or more. **If intubated, give surfactant within the first 48 hrs if in respiratory distress**	**Reintubation Criteria** **Standard of Care**
Extubation Criteria	**Attempt extubation within 24 hours of fulfilling all of the following criteria:** • $PaCO_2$ < 65 torr with a pH > 7.20 (arterial or capillary samples) • An indicated SpO2 $\geq$ 88% with an FiO2 $\leq$ 50% • Mean airway pressure (MAP) < 10 cm H_2O, vent rate $\leq$ 20 bpm, amplitude < 2X MAP if on HFV • Absence of clinically significant PDA • Hemodynamically stable	**Keep intubated and ventilated until criteria met. Attempt extubation within 24 hours of fulfilling all of the following criteria** • $PaCO_2$ < 50 torr and pH > 7.30 (arterial or capillary samples) • FiO2 $\leq$ 35 with SpO2 > 88% • Mean airway pressure (MAP) < 8 cm H_2O, vent. rate $\leq$ 20 bpm, amplitude < 2X MAP on HFV • Absence of clinically significant PDA • Hemodynamically stable
Repeated Surf Doses	Subsequent doses may be given at the manufacturer's recommended dose up to a total of 4 doses.	
Intubation	Intubation may be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery	
CPAP D/C	In room air for at least 1 hour	
CPAP Resumption	At any time	
Duration of Intervention	14 days	14 days

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