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## Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## **Abstract**

### **Objective**

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased after SUPPORT within NICUs in NRN centers.

### **Study Design:**

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation.

### **Results:**

After adjustment for baseline variables, the RR (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval 0.85-0.91) was significantly lower than one.

**Conclusions:**

**After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation compared to infants born before SUPPORT.**

## **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if clinical practice, specifically the proportion of preterm inborn infants intubated in the DR, decreased after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a decrease in ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. The most important secondary outcomes were the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days. We

included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours. The latter criterion was different from SUPPORT, where patients were included if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery,

multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP as of status, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice, Apgar scores, temperature

within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>4</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5-13</sup> Since we did not adjust p-values for multiple comparisons, all secondary and

tertiary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). The primary imbalance was due to outborn status. The study population included 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use, maternal hypertension, maternal diabetes, cesarean section delivery, and less prolonged rupture of membranes in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome the adjusted risk of DR ETI significantly decreased after SUPPORT (Table 2).

For secondary outcomes, the adjusted risk of BPD/death, severe ROP/death, death before discharge, severe ROP, and death or mechanical ventilation at day of life seven were significantly lower in the post-SUPPORT group (Table 2). In contrast, the adjusted risk of BPD and death at 36 weeks were not significantly different between groups. The average number of ventilator days among survivors decreased after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group ( $P < 0.001$ ).

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p = 0.18$ ).

### **Discussion:**

Infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and did not analyze serial changes in the proportion of ETI in each participating center. The proportion of ETI in each center could have decreased with increasing use of CPAP and experience with T-piece connectors before, during or after participation in the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation or after publication of the results of SUPPORT. The proportion of ETI in one of the centers participating in SUPPORT decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ETI in

a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).<sup>16</sup> In another center among the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between the change in the proportion in ETI after SUPPORT and baseline ETI proportion may have resulted from the limited number of centers in this study and from the narrow range (82-97%) of pre-SUPPORT proportions of ETI in 9 of 11 centers.

The strengths of this study include a large sample size, the use of a prospective database and of inborn patients which limits incomplete/missing data and information bias, the use of multivariate analysis to take into account confounding variables, the use of inclusion and exclusion criteria that were similar to those used in SUPPORT, and the inclusion of study centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to large inter-institutional differences that have been observed in previous NRN studies.

Limitations of this study include the observational before/after study design, which prevents any cause-effect interpretation; the high percentage of exclusions; lack of serial data and of data from centers that did not participate in SUPPORT but remained in the NRN during the study period, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; and lack of information in the GDB on DR CPAP, oxygen

saturation, or rationale used for each practice in each infant. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Mortality before discharge decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN<sup>18,19</sup> but is consistent with a recent review among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011.<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21</sup>

This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O<sub>2</sub> delivery or O<sub>2</sub> saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on antenatal, DR and NICU management and outcomes.<sup>22-31</sup> We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. Experience in the network has shown that such surveys often are not very accurate even on current practices.

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might

have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI in preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at NRN Centers after the SUPPORT trial was lower compared to those born during a period before SUPPORT.

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Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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12.

## **Figure Legends**

**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

Figure 1

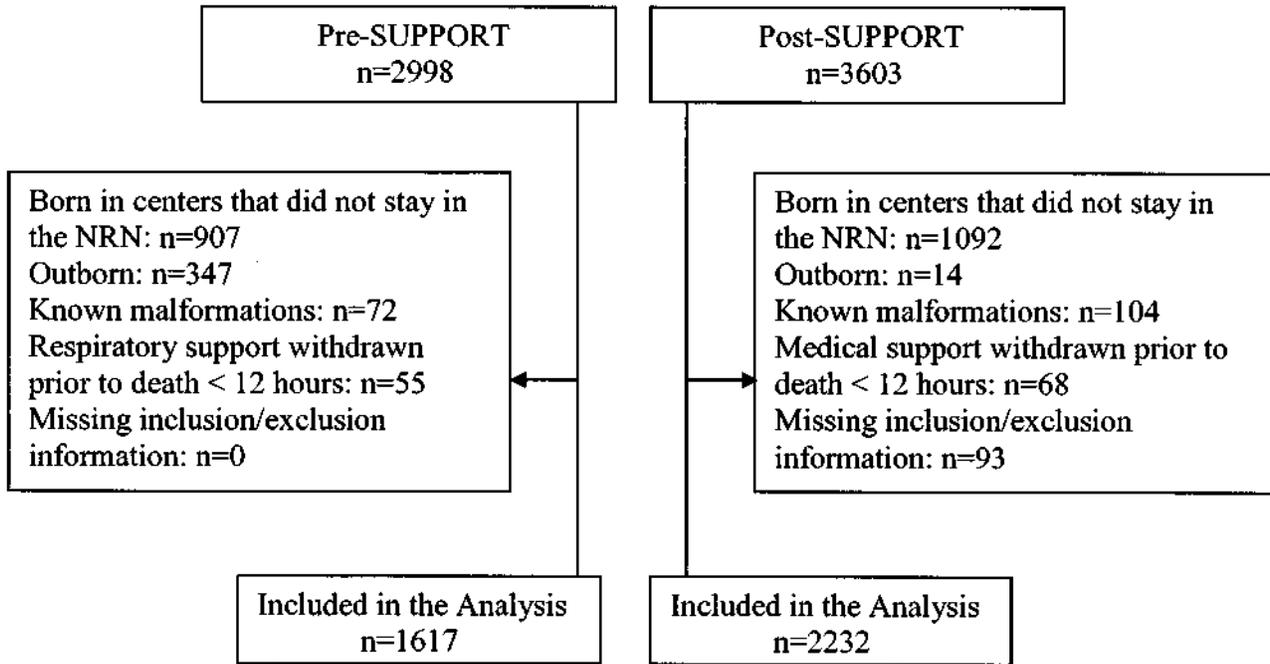
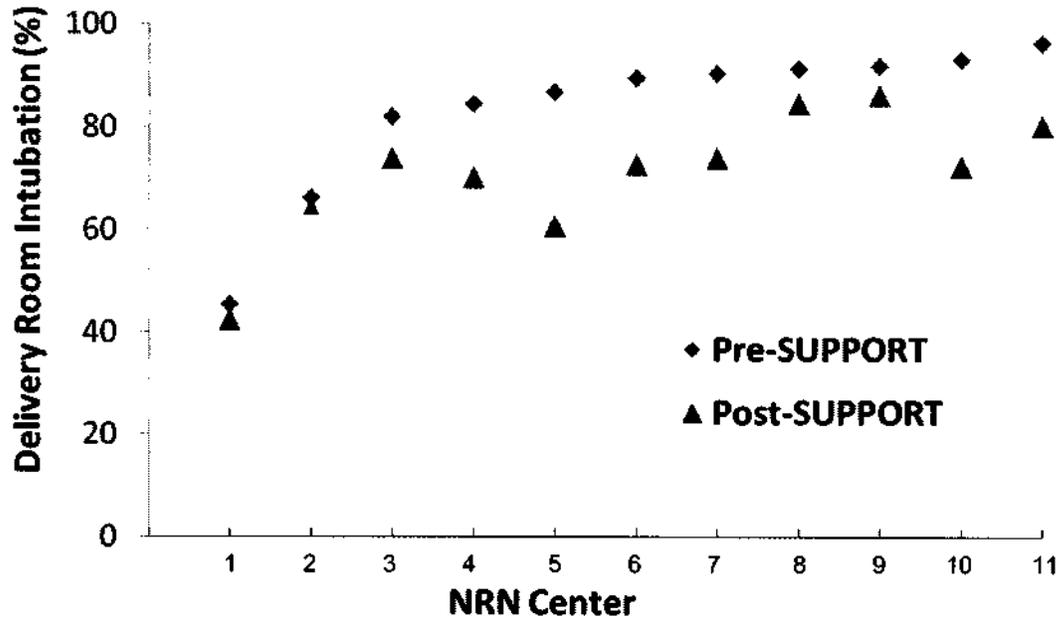


Figure 2



**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192(14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>3</sup></b>
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP <sup>4</sup>	174/1294 (13.5)	181/1875 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.003
Days on ventilator survivors <sup>5</sup>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD as also includes intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> for infants who had an ROP exam with complete information

<sup>5</sup> survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

**Table 3- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup> presented as mean (SD), median for temperature at 60 minutes, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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**First draft:** Dr LeVan wrote the first draft of the manuscript.

**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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**Clinical Trial registration:** NCT00063063 (GDB) and NCT00233324 (SUPPORT)

**Abstract length:** ~~19457250~~ words

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**Revised** ~~119/25328713/13~~

**List of Abbreviations:**

**ARR, Absolute risk reduction;**

**BPD, bronchopulmonary dysplasia;**

**CI, confidence interval;**

**CPAP, continuous positive airway pressure;**

**DR, delivery room;**

**ETI-Endotracheal Intubation;**

**GA, gestational age;**

**GDB, generic database;**

**NRN, Neonatal Research Network;**

**PDA, patent ductus arteriosus;**

**PMA, postmenstrual age;**

**ROP, retinopathy of prematurity;**

**RR, relative risk;**

**SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

## Abstract

### Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased by 15% after compare medical care practices and neonatal outcomes before and after publication of SUPPORT withiwithin NICUs in NRN centers.

### Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)

**Comment [LW1]:** I am not aware that this was our hypothesis, the latest version of the proposal that I have still says that the frequency of DR intubation will decrease post-SUPPORT. I think we should stick with our original statement of hypothesis, we did not address this as currently stated.

I'd be interested to know what Abhik thinks of this change from a general to much more specific hypothesis.

Reading further, it looks like this change was precipitated by a reviewer question about expected effect size, etc., so please see my other various related comments in the paper and also in the document containing responses to reviewers.

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) ~~was~~ were significantly lower than one.

Conclusions:

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, ~~BPD/death, ROP/death and death at discharge~~ compared to infants born before SUPPORT.

**Comment [LW2]:** Correct and this follows from our original hypothesis.

### **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if ~~publication of SUPPORT was temporally associated with changes in~~ clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR, ~~decreased~~ changed after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a 1.5% decrease ~~lower proportion of in~~ ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT, ~~using a conservative estimate based on preliminary data at Parkland Memorial Hospital.~~ We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. ~~The most important neonatal secondary outcomes were se included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes changed after SUPPORT.~~

**Comment [LW3]:** See previous comment about this

**Comment [LW4]:** I think you can use this info somewhere, but I don't think we should change the statement of hypothesis.

## Methods

### Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRR centers) in one birth cohort of patients born before the initiation of the

SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT

Trial.- The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. Data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days. GDB has defined variables with detailed definitions: all patients are followed in GDB to ascertain all listed outcomes. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

**Comment [LWS]:** This sentence is awkward, suggest something like: The GDB collects detailed maternal pregnancy/delivery data and baseline, treatment and outcome data on infants using standardized protocols and forms. (if we have more room we can give more detailed information such as data is collected to death, discharge, or 120 days ('status'), whichever comes first, and limited additional data is collected on infants who remain in the hospital at 120 days.) Something like this could also help with the question of timing of birth and ascertaining outcomes which one reviewer raised.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain ~~about~~ similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar ~~but not identical~~ to those used in SUPPORT<sub>5-1,2</sub>. Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

The latter criterion was different from SUPPORT, where patients were in~~ex~~cluded if a decision had been made to provide full resuscitation for them.

#### Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

#### Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important sSecondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP as of status, at discharge, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for

**Comment [LW6]:** I don't think this 'and' should be deleted.

positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): ~~BPD, severe ROP and other ROP outcomes~~, death within 12 hours or by 36 weeks PMA, DR ~~practice outcome~~, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

#### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal

corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>46</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5137-156</sup> Since we did not adjust  $p$ -values for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). The primary imbalance was due to outborn status. T~~Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn.~~

**Comment [LW7]:** I don't think we need to put this section in the paper, this was done (I think) to justify the study for the Network (i.e. do we have the data to make it worth doing, which we did). Otherwise is it really relevant? I am not sure it is. It also looks like this might be where that 15% reduction in risk is coming from (or I guess that was the result from the single center study), again I don't think that was part of the original hypothesis. I think that you were just trying to show that you'd have enough data to show a clinically relevant reduction?

~~Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a he total study population included of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.~~

~~The baseline maternal and neonatal characteristics of both groups are shown in Table 11. There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.~~

~~For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT (Table 2).~~

~~For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 22). In contrast, the adjusted risk~~

**Comment [LW8]:** I am not sure that we need to state both unadjusted and adjusted outcome results. Maybe we could just say that results for primary and secondary outcomes are shown in Table 2 and go on to discuss adjusted results.

of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only, the appendix. Several differences were observed between the two periods. Post hoc analysis showed that the proportion of babies who were never intubated was 5.6% for the Pre-SUPPORT group, and 11.4% for the Post-SUPPORT group (P<0.001).

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Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

#### **Discussion:**

Infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was four times as large as the ARR in DR ETI observed in very low birth weight infants in the Vermont Oxford Network over a 10-year span between 2000 and 2009 (3.7%; 95% CI 4.2% to 3.3%).<sup>18</sup> The ARR over a 10-year span in the NRN and Vermont Oxford Network was

~~less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%).~~ In this study we compared data before SUPPORT with data after SUPPORT and did not ~~thus we were unable to analyze serial changes in whether the decrease in~~ proportion of ETI in each participating centers. The proportion of ETI in each center could have decreased ~~with increasing use of CPAP and experience with took place at the time of introduction of and increasing experience with T-piece connectors before, during or after participation in ,~~ ~~conduction of the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation the trial, or after publication of the results of SUPPORT.~~ The proportion of ETI in ~~at Parkland Memorial Hospital, one of the centers participating in SUPPORT;~~ decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010), in the absence of any change in DR policy or practice guideline. The proportion of ~~ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009),<sup>16</sup> In another center among one of the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after the neonatologists prospectively introduced routine, early, bubble nasal CPAP~~ ~~introduction of bubble CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between~~ ~~We had hypothesized that the change in the proportion in ETI after SUPPORT and would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study and from the~~

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narrow range (82-97%) of and from the fact that 9 of the 11 centers had pre-SUPPORT proportions of ETI in 9 of 11 centers that varied within a narrow range of about 82-97%. and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database and of inborn patients which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods, the use of inclusion and exclusion criteria that were similar to resembled (though did not exactly match) those used in SUPPORT, and the inclusion of We were able to analyze center specific changes after SUPPORT as well as changes in the entire sample, because we only used We elected to limit for this study to centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to l; because of large inter-institutional differences that have been observed in previous NRN

~~studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample.~~

However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which prevents any cause-effect interpretation; the which could introduce changes in patient population; ~~strict selection criteria~~high percentage of exclusions; lack of serial data and of data from centers that did not participate in SUPPORT but remained in the NRN during the study period, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; ~~the limited number of variables included in the GDB, and secular trends~~and lack of information in the ~~the~~ Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in the primary outcomes of SUPPORT. In this study we compared data before SUPPORT with data after

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~~SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p-value < 0.05 just by chance; thus p-values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB on did not include information on individual use of DR CPAP, oxygen saturation targets in the DR or the NICU, or the rationale used for each various practice in each infant, s used for each patient in each center. It is also possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.~~

~~Since we did not adjust p-value for multiple comparisons, secondary and tertiary variables should all be considered as exploratory. Mortality The risk of death before discharge was significantly decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>19</sup> and between 2003 and 2007.<sup>18,19,20</sup> but It is consistent with a recent review a recent review of deaths among extremely low~~

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~~birthweight infants enrolled in the GDB which showed a decrease in mortality among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011.<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21,24</sup>~~

~~This study was not designed to test whether any change in secondary or tertiary variables were associated with DR ETI, with changes in O2 delivery or O2 saturation targets or limits, or with the application in practice of evidence from SUPPORT or from other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies.~~

~~We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since serial oxygen saturation measurements were not prospectively collected in the GDB before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Several center-specific practice guidelines and policies may have individual practice may have changed between the two epochs, based on new information on other studies rather than SUPPORT, e.g., antenatal DR studies on and NICU management and outcomes antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive pressure ventilation,<sup>26</sup> prevention of central line~~

~~associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>22-31,39,29</sup> We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to do so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. Experience in the network has shown that such surveys often are not very accurate even on current practices. DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>300</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies.~~

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors and with tight oxygen monitoring during SUPPORT and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ~~ROP/death, BPD/death, and death before discharge in~~ for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at ~~NRN Network Centers was lower after following the publication of the~~ SUPPORT trial was lower compared to those born during a period before SUPPORT. ~~the~~

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~~adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.~~

~~Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.~~

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**Acknowledgments:**

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**Jaelyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Luc P Brion:** Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

**Lisa Wrage:** Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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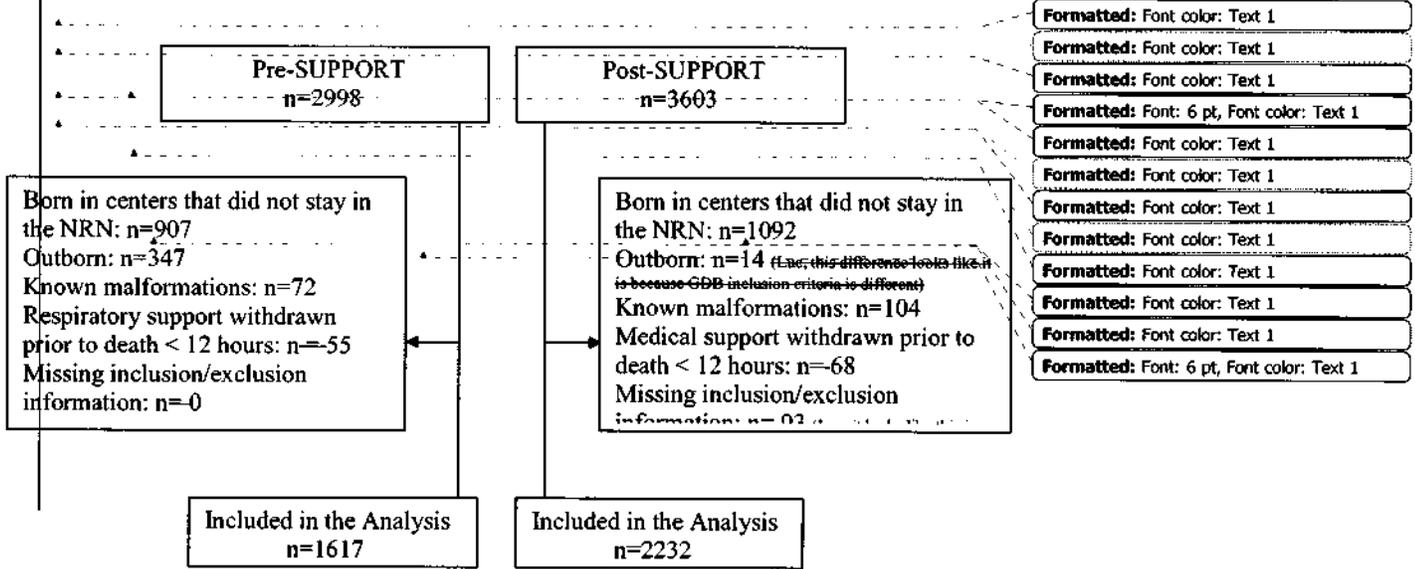
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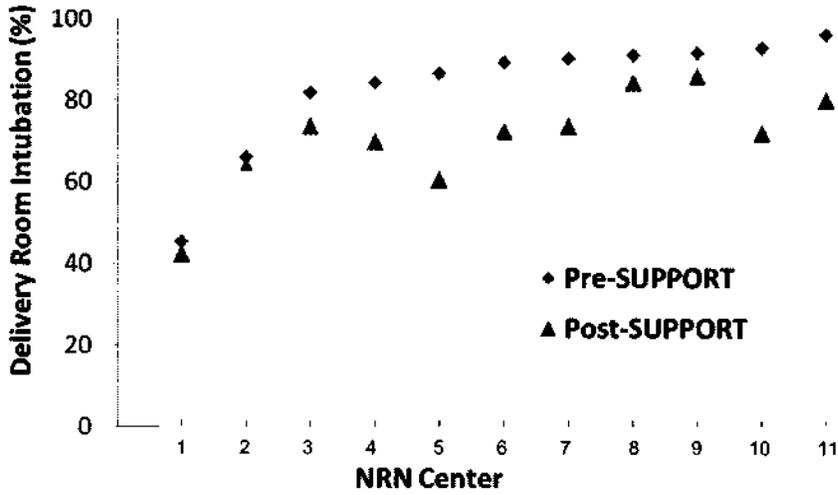
**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

Figure 1



**Figure 2**



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**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
<b>Race/ethnicity:</b>			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192 (14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120/2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

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Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup> The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>3d</sup></b>
<b>Intubated in delivery room (primary outcome)</b>	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
<b>BPD or death at 36 weeks</b>	970/1617 (60.0)	1199/2213 (54.2)	0.0003	=	0.94 (0.89-0.99)	0.02
<b>Severe ROP or death</b>	515/1581 (32.6)	559/2165 (25.8)	<0.0001	=	0.81 (0.73-0.89)	<0.0001
<b>Death before discharge</b>	358/1614 (22.2)	393/2196 (17.9)	0.001	=	0.86 (0.76-0.98)	0.02
<b>Bronchopulmonary dysplasia (36 weeks)</b>	664/1311 (50.7)	855/1869 (45.8)	0.0064	=	1.04 (0.97-1.1)	0.26
<b>Severe ROP<sup>4</sup> by discharge</b>	174/1294 (13.5)	181/18753 (9.7)	0.0009	=	0.63 (0.52-0.77)	<0.0001
<b>Death by 36 weeks</b>	306/1617 (18.9)	344/2222 (15.5)	0.0050	=	0.88 (0.76-1.00)	0
<b>Death or mechanical ventilation on day 7</b>	741/1613 (45.9)	875/2211 (39.6)	<0.0001	=	0.90 (0.84-0.97)	0
<b>Days on ventilator (survivors<sup>5d</sup>) until discharge</b>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

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**Comment [LW9]:** Luc, Severe ROP is defined for infants who had an ROP exam with complete information

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup>presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup>adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models, taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FIO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis. <sup>3d</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

All models include GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as also includes intubation in the DR, surfactant, FIO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> for infants who had an ROP exam with complete information

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<sup>5d</sup>survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

|

**Table 3- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1), 35.9	36.5 (0.8), 36.5	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36.4)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup>presented as mean (SD), median for temperature at 60 minutes, for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup>The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup>survivors to discharge, transfer, or 120 days, whichever came first, max is 120 days.

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Manuscript Draft

Manuscript Number:

Title: Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Article Type: Original Article

Keywords: very preterm; endotracheal intubation; delivery room; bronchopulmonary dysplasia; retinopathy of prematurity; mortality

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**Abstract: Objective**

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 240/7-276/7 weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after publication of SUPPORT within NICUs in NRN centers.

**Study Design:**

This was a retrospective cohort study using the prospective NRN generic database. We included infants 240/7-276/7 weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

**Results:**

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 240/7-276/7 weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.



Department of Pediatrics  
Division of Neonatal-Perinatal Medicine

Monday, September 12, 2013

William F. Balistreri, MD  
The Journal of Pediatrics  
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Cincinnati, OH 45229-3039

Dear Dr. Balistreri:

We would like to submit an original manuscript entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" for publication in Journal of Pediatrics.

We have previously submitted to Pediatrics a related manuscript, which was just accepted for publication. In that manuscript, entitled "Change in Process of Care Among Non-Enrolled Patients During and After a Randomized Trial" we had assessed changes in delivery room intubation at Parkland Memorial Hospital during SUPPORT and before publication of SUPPORT in comparison to a period before SUPPORT (January 2003-June 2005). This manuscript is described in the discussion of current manuscript (reference 21). The current manuscript assesses changes in clinical practice and outcome in the NICHD Neonatal Research Network after publication of the SUPPORT Trial in comparison with those before SUPPORT. Parkland Memorial Hospital was part of the NICHD Network during the period of the study. Therefore, data from patients born at Parkland Memorial Hospital before SUPPORT (1/1/2003-12/31/2004) are included along with those in 10 other NICHD Neonatal Research Network centers in the current manuscript. Since data from patients born at Parkland Memorial Hospital before SUPPORT (1/1/2003-12/31/2004) are included in both manuscripts, we have uploaded the proof of the manuscript in press in Pediatrics along with the current submission.

The manuscript has not been and will not be submitted to any other journal while it is under consideration by Journal of Pediatrics.

There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Dr. Jaclyn LeVan wrote the first draft of the manuscript.

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Contributions of each authors are provided below:

**Jaclyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Luc P Brion:** Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr. Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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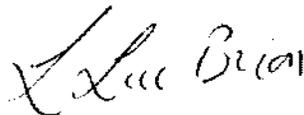
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We respectfully request to consider the attached manuscript for publication in Journal of Pediatrics. We believe this manuscript describes a study with strong design, which brings novel and significant findings that are relevant to the readership of Journal of Pediatrics.

Sincerely,



**Luc P. Brion, MD**

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Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
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No reprints needed

**First draft:** Dr LeVan wrote the first draft of the manuscript.

**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

**Funding source:** NICHD

**Financial Statement:** No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

**Conflict of Interest Statement:** There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

**Clinical Trial registration:** NCT00063063 (GDB) and NCT00233324 (SUPPORT)

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**List of Abbreviations:**

**BPD, bronchopulmonary dysplasia;**

**CI, confidence interval;**

**CPAP, continuous positive airway pressure;**

**DR, delivery room;**

**ETI-Endotracheal Intubation;**

**GA, gestational age;**

**GDB, generic database;**

**NRN, Neonatal Research Network;**

**PDA, patent ductus arteriosus;**

**PMA, postmenstrual age;**

**ROP, retinopathy of prematurity;**

**RR, relative risk;**

**SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

## **Abstract**

### **Objective**

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after publication of SUPPORT within NICUs in NRN centers.

### **Study Design:**

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### **Results:**

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

### **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

### Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

### Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

### Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was ETI in DR.

Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes  $> 24$  hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>7-16</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1.

There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 2). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in the appendix. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p=0.18$ ).

### **Discussion:**

Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast

with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces

confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB did not include information on the rationale used for various practices used for each patient in each center. We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and

changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive-pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies. This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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## **Figure Legends**

**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

**Table**

**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Difference in Means <sup>3</sup> (95% CI)	adjusted RR <sup>3</sup> (95% CI)	Adjusted p value <sup>4</sup>
Intubated in delivery room (primary outcome)	1313 (81.2)	1539 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

Table

**Appendix. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.0028
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

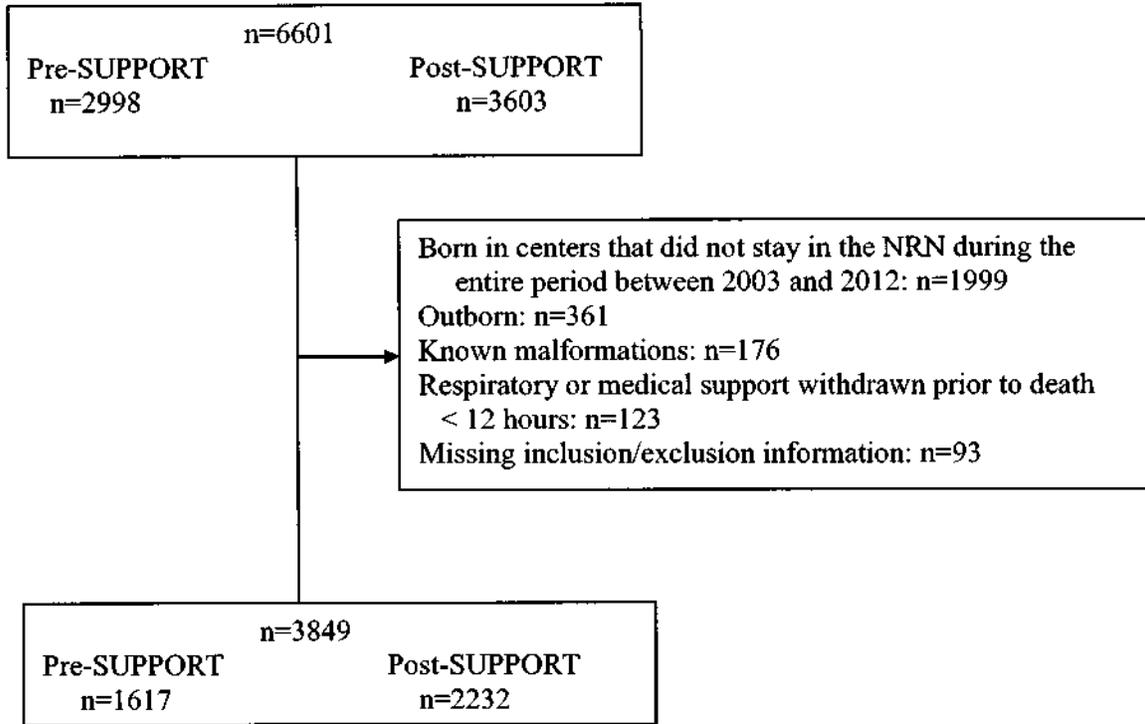
<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

**Figure**

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**Figure 1**



# Change in Care Among Nonenrolled Patients During and After a Randomized Trial

Q:1,2,3

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## KEY WORDS

randomized controlled trial, process of care, unblinded, preterm, endotracheal intubation, birth cohort study, non-enrolled patients

## ABBREVIATIONS

BW—birth weight

CI—confidence interval

CPAP—continuous positive airway pressure

DR—delivery room

GA—gestational age

NNT—number needed to treat

NRN—Neonatal Research Network

PMH—Parkland Memorial Hospital

RCT—randomized controlled trial

RD—risk difference

RR—relative risk

SUPPORT—Surfactant, Positive Pressure, and Oxygenation Randomized Trial

VON—Vermont Oxford Network

Dr LeVan conceptualized and designed the study, merged data from all Parkland Memorial Hospital (PMH) databases, participated in the interpretation of the data, drafted the first version of the manuscript, and critically reviewed the revisions; Drs Wyckoff, Heyne, Sanchez, Chalak, and Jaleel conceptualized and designed the study, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Ahn conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Ms Burchfield and Ms Christie collected and entered data into the databases and extracted the data for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Soll conceptualized and designed the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Badger conceptualized, designed, and conducted the statistical analyses for the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Brion conceptualized and designed the study, conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)



**WHAT'S KNOWN ON THIS SUBJECT:** Participating in a trial may affect processes of care by participating physicians; however, no study has assessed whether it affects processes of care for nonenrolled patients.



**WHAT THIS STUDY ADDS:** Participation in a trial may affect processes of care for nonenrolled patients, even when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study.

**OBJECTIVE:** Parkland Memorial Hospital (PMH) participated in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded controlled trial, in which preterm neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' gestational age (GA) were randomized in the delivery room (DR) to endotracheal intubation or nasal continuous positive airway pressure. We hypothesized that DR intubation could change in nonenrolled patients at PMH and that the change would be larger than in comparable centers not participating in the trial.

**METHODS:** The PMH Cohort included eligible but nonenrolled neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks (primary) and noneligible neonates of 28 to 34<sup>6/7</sup> weeks (confirmatory). A subset (24<sup>0/7</sup>–29<sup>6/7</sup> weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in the Vermont Oxford Network (VON). We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation (during/after SUPPORT versus before SUPPORT) for PMH and for VON along with the ratio of these RRs.

**RESULTS:** In the PMH cohort ( $n = 3527$ ), the proportion of DR intubation decreased during/after SUPPORT in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96) and the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70). Compared with the RR for DR intubation in VON, the RR at PMH was smaller in the lower (ratio of RR 0.76, 95% CI 0.65–0.87) and the upper GA group (ratio of RR 0.52, 95% CI 0.39–0.68).

**CONCLUSIONS:** A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. *Pediatrics* 2013;132:1–11

Q-6

Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients.<sup>1,2</sup> Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.<sup>1</sup> Andersen et al showed that conducting a seeding trial (company-driven trial to entice doctors to prescribe a new drug being marketed by the company) changed some processes of care among participating physicians compared with nonparticipating physicians; however, processes of care for nonenrolled patients were not assessed.<sup>3,4</sup>

The objective of the current study was to evaluate whether a process of care of contemporaneous nonenrolled patients can change during and after recruitment to an unblinded randomized trial, when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study. We hypothesized (1) that participation of Parkland Memorial Hospital (PMH) in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded RCT comparing processes of care, could be associated with a reduction in the proportion of delivery room (DR) intubation in nonenrolled patients, and (2) that the local practice change would be larger than in comparable centers not participating in SUPPORT.

## METHODS

### Setting

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 × 2 factorial trial in which preterm neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' gestational age (GA) were randomized at birth to 2 interventions:

(1) continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration, and (2) oxygen saturation targets of 85% to 89% or 91% to 95%.<sup>5,6</sup> The first intervention (CPAP versus DR intubation/surfactant) was unblinded, and its primary outcome was death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age.<sup>5</sup> PMH participated in SUPPORT from July 2005 until February 2009.

Data were compiled from 3 prospective databases, including detailed information about DR and NICU management with predetermined entry criteria and definitions: the Neonatal DR Resuscitation Registry (started in 1989), the NICU database (started in 1977), and SUPPORT registry. At PMH, all neonates <35 weeks' GA by obstetrical assessment are admitted to the NICU and included in the Resuscitation Registry and in the NICU database (unless triaged to the newborn nursery if pediatric assessment is >34 weeks' GA and the infant is otherwise well). These databases provide information on 99.8% of eligible neonates, with high interrater reliability (<1% error); most missing data points correspond to infants triaged to the newborn nursery (≤6%).

Data for an analysis cohort were abstracted by using a before–after study design during 3 consecutive epochs: (1) up to 30 months before SUPPORT initiation, (2) during SUPPORT participation, and (3) up to 15 months after trial completion. To account for secular trends in DR intubation, a subset of the PMH cohort was compared with a contemporaneous control population in the Vermont Oxford Network (VON), a voluntary collaboration of more than 900 NICUs around the world. The VON includes de-identified data by calendar year on infants with birth weight (BW)

of 501 to 1500 g. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

### Participants

The PMH cohort included neonates 24<sup>0/7</sup> to 34<sup>6/7</sup> weeks' GA born at PMH before SUPPORT (January 2003–June 2005), during SUPPORT (July 2005–February 2009), and after SUPPORT (March 2009–June 2010) until SUPPORT publication.<sup>5,6</sup> The study included (1) neonates 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' GA who were eligible for SUPPORT but not enrolled (lower GA group), and (2) noneligible neonates of 28<sup>0/7</sup> to 34<sup>6/7</sup> weeks' GA (upper GA group). The latter was used as a positive control for the lower GA group, in whom selection bias (due to exclusion of patients enrolled into SUPPORT) was possible.<sup>7,8</sup> Exclusion criteria were comfort care or major congenital anomalies known at birth, lack of patient record in the DR Resuscitation Registry or the NICU database, and enrollment in SUPPORT.

A subset of the PMH cohort, including all neonates 24<sup>0/7</sup> to 29<sup>6/7</sup> weeks' GA born in 2003 to 2004 (before SUPPORT) and 2006 to 2009 (during/after SUPPORT), was compared with inborn contemporaneous neonates born in level IIIb or IIIc North American centers participating in VON. The subset included (1) neonates 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' GA (lower GA group), and (2) neonates of 28<sup>0/7</sup> to 29<sup>6/7</sup> weeks' GA (upper GA group). We excluded centers participating in SUPPORT or in the VON Delivery Room Management Trial,<sup>9</sup> and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies. This GA range was selected because infants in this GA range are included in the 501 to 1500 g BW range of VON. PMH was not a member of VON during the study period.

## Comparisons of Interest

### *PMH Cohort*

The primary analysis was the adjusted relative risk (RR) of DR intubation during/after SUPPORT versus before SUPPORT in the lower GA group. The adjusted RR in the upper GA group was confirmatory and used as a positive control.

Univariate analyses in each GA group evaluated DR treatment (endotracheal intubation, positive pressure ventilation, CPAP), intubation (within the first 4 hours after admission to the NICU or during the first 24 hours of age), surfactant administration, pneumothorax, mortality to discharge from the hospital, chronic lung disease (chronic changes on chest radiograph and supplemental oxygen requirement for at least 28 days), duration of mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis (stage II or greater, modified Bell classification),<sup>10</sup> severe intraventricular hemorrhage (Papile grade III or IV),<sup>11</sup> periventricular leukomalacia, and severe retinopathy of prematurity (grade 3 or higher, international classification).<sup>12</sup>

### *Comparison With VON*

The primary analysis was the comparison of RR (adjusted for baseline variables) of DR intubation (during/after SUPPORT versus before SUPPORT) in the subset of the PMH cohort in the lower GA group with the RR of DR intubation in the contemporaneous VON cohort.

The secondary analyses were (1) the adjusted ratio of RRs for DR intubation in the upper GA group and (2) the adjusted ratio of RRs for any invasive (endotracheal tube or tracheostomy) ventilation.

## Statistical Analysis: PMH Cohort

### *Multivariate Analyses*

In each GA group, the adjusted RRs for DR intubation during/after SUPPORT versus before SUPPORT were calculated using robust Poisson regression in a generalized estimating equation model adjusted for covariates that met the  $P < .05$  criterion (backward selection). Candidate variables selected for modeling were characteristics preceding the decision of DR intubation and shown previously to associate with DR intubation.<sup>13–27</sup> To avoid collinearity with GA, BW was converted to BW z-score.<sup>28</sup> The adjusted risk difference (RD) and number needed to treat (NNT) were obtained from the adjusted RR and the proportion of DR intubation before SUPPORT. The Altman interaction test<sup>29</sup> was used to determine if the adjusted RRs for DR intubation were different between GA groups.

### *Univariate Analyses*

Univariate analyses were performed by using  $\chi^2$  tests or Fisher's exact tests for categorical variables, and Student's *t* tests or analyses of variance followed by Tukey test, or Kruskal-Wallis test followed by Mann-Whitney test for continuous variables. We analyzed temporal patterns of DR intubation to determine how soon after initiating SUPPORT the proportion of DR intubation changed from baseline; we selected blocks of 15 to 16 months to limit fluctuation due to sample size.

Statistical analyses were performed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance (2-tailed) was determined based on  $P < .05$ , except for multiple pairwise non-parametric comparisons, for which we used the Bonferroni adjustment.

The time interval for data abstraction was set to ascertain a sufficient number

of registered patients in the PMH cohort to detect changes in DR intubation in the lower GA subgroup using multivariate analysis. Given the ascertainment of data on 200 DR intubations, the analysis set was sufficient to conduct a multivariate analysis with up to 20 independent covariates tested as main effects, with a 2-sided  $\alpha$  of 0.05. The duration of the study was set to recruit enough patients to detect changes in DR intubation in the lower GA group by univariate analysis. The effect size was selected as a 33% RR reduction in DR intubation, a conservative estimate compared with the 47% RR reduction in DR intubation in a center in which routine DR bubble CPAP was prospectively introduced in 2000.<sup>21</sup> A sample of 97 patients before SUPPORT and during/after SUPPORT yielded 80% power to detect a reduction in DR intubation from 60% to 40% with a 2-sided  $\alpha$  of 0.05.

### *Comparison With VON*

A Poisson regression model with robust variance was used for each GA group to obtain adjusted RRs (during/after SUPPORT versus before SUPPORT) for PMH and VON along with the ratio of their RRs.<sup>30</sup> Covariates in the model were infants' GA, gender, BW, z-score, and antenatal steroids. Location (PMH and VON) and epoch (before and during/after SUPPORT) were represented by a 4-level categorical variable in the model, with the appropriate linear contrasts constructed to obtain estimates of RRs and their ratio.

## RESULTS

### **PMH Cohort**

At PMH, a total of 3821 individual patient database records were reviewed, of which 3533 were eligible and 3527 (99.8%) had records in the 3 PMH databases (Fig 1). The analysis cohort comprised 3527 records. In the lower GA group, the percentage of multiple

births was lower after SUPPORT (Table 1). In the upper GA group, exposure to antenatal steroids was more frequent after SUPPORT, maternal diabetes was more frequent during SUPPORT, and BW was greater during/after SUPPORT; other differences were clinically insignificant (Table 2).

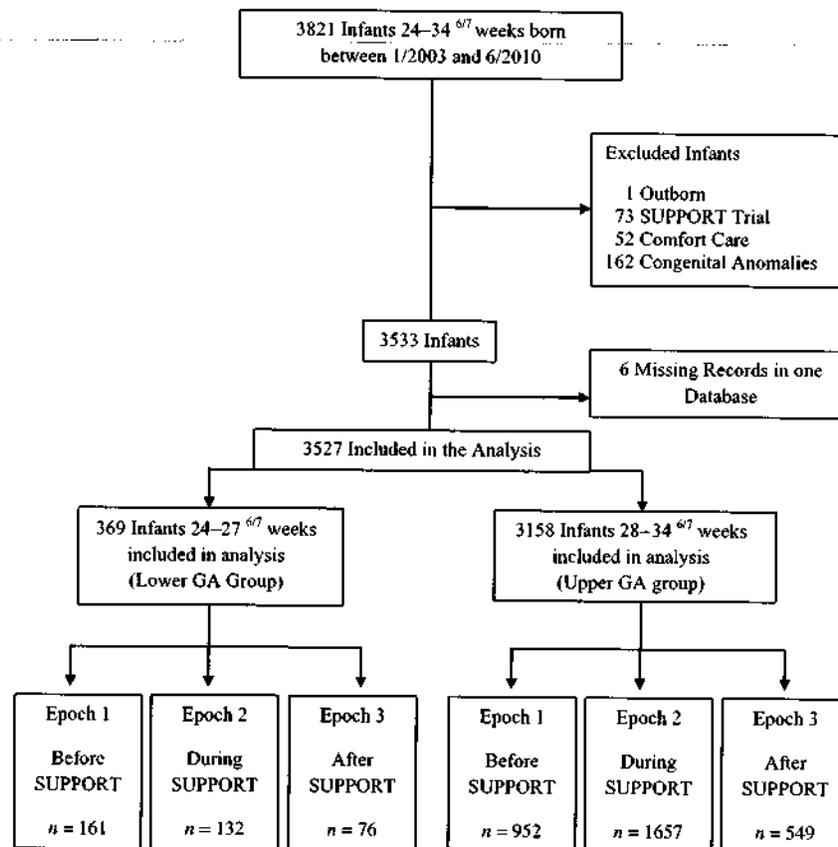
During SUPPORT, patients in the lower GA group included in the current study had a greater GA than contemporaneous patients enrolled in SUPPORT (excluded from the current study), were less likely to have been exposed to antenatal steroids, and were more likely to receive positive pressure ventilation in the DR (Appendix).

#### Multivariate Analysis

Among 3527 neonates, 649 (18%) were intubated in the DR. The proportion of DR intubation significantly decreased during/after SUPPORT versus before SUPPORT, in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96,  $P = .02$ ) and in the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70,  $P < .001$ ) (Tables 3 and 4). In the lower GA group, the proportion of DR intubation decreased from 85% before SUPPORT to 61% during/after SUPPORT (Table 5) (adjusted RD 0.21, 95% CI 0.03–0.34; NNT 5, 95% CI 3–33). In the upper GA group, the proportion decreased from 19% to 10% (Table 6) (adjusted RD 0.08, 95% CI 0.06–0.10; NNT 12, 95% CI 10–18). The decrease in DR intubation was not significantly different in the upper GA group compared with the lower GA group (adjusted ratio of RR 0.75, 95% CI 0.54–1.03).

#### Univariate Analyses

In the lower GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ( $P = .01$ ) and that of CPAP increased ( $P < .001$ ) (Table 5). Not surprisingly, the proportion of intubation in the NICU within



**FIGURE 1**  
Flow diagram at PMH.

**TABLE 1** Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010. Q:10  
Lower GA Group: 24<sup>6/7</sup> to 27<sup>6/7</sup> Weeks' Gestation

Characteristic <sup>a</sup>	Before SUPPORT, n = 161	During SUPPORT, n = 132	After SUPPORT, n = 76	P Value
GA, wk, mean (SD)	25.8 (1.0)	25.9 (1.1)	25.8 (1.1)	.42
BW, g, mean (SD)	858 (236)	908 (238)	874 (290)	.24
Size for age, n (%)				.52
Small for GA	19 (12)	14 (11)	10 (13)	
Large for GA	19 (12)	25 (19)	12 (16)	
Female, n (%)	74 (46)	61 (46)	36 (47)	.98
Multiple birth, n (%)	34 (21)	19 (14)	5 (7)*	.01
Antenatal steroids, n (%)	81 (50)	52 (39)	38 (50)	.14
Abruptio placentae, n (%)	6 (4)	11 (8)	4 (5)	.25
Placenta previa, n (%)	3 (2)	1 (1)	3 (4)	.25
Maternal diabetes mellitus, n (%)	6 (4)	10 (8)	8 (11)	.11
Gestational hypertension or preeclampsia, n (%)	25 (16)	28 (21)	19 (25)	.19
Clinic attendance, n (%)	146 (90)	113 (86)	67 (88)	.40

<sup>a</sup> Complete data were available for patients in the lower GA group and for GA. P values on the last column on the right are based on analyses of variance or  $\chi^2$  analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined using  $P < .025$  and P values indicated as \*  $P < .025$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

4 hours after admission increased over time ( $P = .03$ ); however, intubation within 24 hours of life decreased

during/after SUPPORT ( $P = .002$ ). The proportion of surfactant administration decreased during SUPPORT ( $P <$

**TABLE 2** Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation

Characteristic <sup>a</sup>	Before SUPPORT, n = 952	During SUPPORT, n = 1657	After SUPPORT, n = 549	P Value
GA, wk, mean (SD)	32.1 (1.8)	32.2 (1.8)	32.4 (1.8)*	.002
BW, g, mean (SD)	1824 (468)	1904 (486)*	1932 (472)*	<.001
Size for age, n (%)				.04
Small for GA	101 (11)	139 (9)	49 (9)	
Large for GA	103 (11)	239 (15)	64 (12)	
Female, n (%)	422 (46)	716 (44)	247 (46)	.64
Multiple birth, n (%)	182 (19)	333 (20)	122 (22)	.35
Use of antenatal steroids, n (%)	260 (27)	430 (26)	204 (37)**	<.001
Abruptio placentae, n (%)	23 (2)	41 (2)	11 (2)	.82
Placenta previa, n (%)	18 (2)	33 (2)	14 (3)	.66
Maternal diabetes mellitus, n (%)	88 (9)	216 (13)*	71 (13)	.01
Gestational hypertension or preeclampsia, n (%)	264 (28)	511 (30)	168 (31)	.23
Clinic attendance, n (%)	852 (90)	1530 (92)*	511 (93)*	.02

<sup>a</sup> In the upper GA group, 95% of data were available; we used the total number available as denominator. P values on the last column on the right are based on analyses of variance or  $\chi^2$  analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined using  $P < .025$  and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

**TABLE 3** Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Lower GA Group: 24<sup>0/7</sup> to 27<sup>6/7</sup> Weeks' Gestation, n = 362

Variable	Adjusted RR <sup>a</sup>	P Value
During/after SUPPORT versus before SUPPORT <sup>b</sup>	0.76, 95% CI 0.59–0.96	.02
Positive pressure ventilation in the DR	3.61, 95% CI 2.02–6.45	<.001

For each categorical variable, the reference group is factor not present; for SUPPORT the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, and cord pH.

<sup>a</sup> Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

<sup>b</sup> Primary analysis.

**TABLE 4** Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation, n = 2742

Variable	Adjusted RR <sup>a</sup>	P Value
During/after SUPPORT versus before SUPPORT <sup>b</sup>	0.57, 95% CI 0.46–0.70	<.001
Positive pressure ventilation in the DR	6.29, 95% CI 4.73–8.37	<.001
GA (per wk)	0.74, 95% CI 0.70–0.78	<.001
Gestational hypertension or preeclampsia	0.72, 95% CI 0.56–0.92	.009
Z score of BW for GA and gender	0.91, 95% CI 0.83–1.00	.046

For each categorical variable, the reference group is factor not present; for SUPPORT, the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, and cord pH.

<sup>a</sup> Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

<sup>b</sup> Confirmatory analysis (positive controls).

.001). The proportion of pneumothoraces increased after SUPPORT ( $P = .03$ ). Most pneumothoraces occurred in neonates who were intubated in the DR.

In the upper GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ( $P =$

.002) (Table 6). The proportion of intubation within 24 hours of life decreased during/after SUPPORT ( $P < .001$ ). The proportion of surfactant administration decreased during SUPPORT ( $P < .025$ ).

Most of the other outcomes except retinopathy of prematurity did not

change during or after SUPPORT. The percentage of DR intubation did not change during baseline in either GA group (Fig 2). In the lower GA group, the proportion of DR intubation decreased within 15 months of SUPPORT, whereas in the upper GA group, it did not significantly change until later.

### Comparison Between PMH and VON

We compared data from 576 neonates born at PMH with data from 85 118 contemporaneous neonates born in 1 of 396 North American VON centers (Table 7).

In the lower GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT at PMH (82% vs 60%; adjusted RR 0.74, 95% CI 0.64–0.86) and in VON (85% vs 84%; adjusted RR 0.98, 95% CI 0.98–0.99). The decrease was greater at PMH than in VON (adjusted ratio of RR 0.76, 95% CI 0.65–0.87). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in the VON data. The change over time was not significantly different between PMH and VON.

In the upper GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT both at PMH and in VON. The decrease was greater at PMH than in VON (adjusted ratio of RR 0.52, 95% CI 0.39–0.68). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in VON. The change over time was not significantly different between PMH and VON.

### DISCUSSION

In the current study, a change in care process (proportion of DR intubation) was observed in eligible but non-enrolled patients and in noneligible

**TABLE 5** Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: 24<sup>0/7</sup> to 27<sup>6/7</sup> Weeks' Gestation

Care Process or Outcome Variable <sup>a</sup>	Before SUPPORT, n = 161	During SUPPORT, n = 132	After SUPPORT, n = 76	P Value
Intubation in the DR, n (%)	136 (85)	81 (61)**	46 (61)**	<.001
Positive pressure ventilation in the DR, n (%)	140 (91)	106 (80)*	60 (79)*	.01
CPAP in DR, n (%)	48 (31)	74 (56)**	48 (63)**	<.001
Intubation in the NICU within the first 4 h after admission to the unit, n (%)	7 (4) <sup>b</sup>	14 (11)	10 (13)	.03
Intubation during the first 24 h of life, n (%)	141 (88)	95 (72)**	56 (73)*	.002
Surfactant, n (%)	121 (79)	78 (59)**	50 (66)	.001
Pneumothorax, n (%)	11 (7)	13 (10)	14 (18)*	.03
Death before discharge, n (%)	43 (27)	34 (26)	18 (24)	.91
Chronic lung disease, n (%)	83 (52)	61 (46)	43 (57)	.34
Total no. days intubated (endotracheal tube or tracheostomy) (n = 338); median (quartiles) <sup>c</sup>	10 (2–23)	5(1–14)	11 (2–29)	.05
Patent ductus arteriosus, n (%)	77 (48)	61 (46)	39 (51)	.78
Necrotizing enterocolitis, stage ≥2, n (%)	14 (9)	10 (8)	5 (7)	.91
Intraventricular hemorrhage, grade 3 or 4, n (%)	25 (16)	20 (15)	18 (24)	.25
Periventricular leukomalacia, n (%)	9 (6)	7 (5)	5 (7)	.92
Retinopathy of prematurity, stage ≥3, n (%)	30 (19)	12 (9)	14 (18)	.04

P values in the last column on the right are based on  $\chi^2$  analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined by using  $P < .025$ , and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

<sup>a</sup> Complete data were available for patients in the lower GA group and for GA<sub>2</sub>.

<sup>b</sup> Two patients, initially intubated in the DR, were intubated again within 4 h after admission in the NICU after a trial on CPAP.

<sup>c</sup> Kruskal-Wallis tests.

**TABLE 6** Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation

Care Process or Outcome Variable <sup>a</sup>	Before SUPPORT, n = 952	During SUPPORT, n = 1657	After SUPPORT, n = 549	P Value
Intubation in the DR, n (%)	177 (19)	162 (10)**	47 (9)**	<.001
Positive pressure ventilation in the DR, n (%)	332 (36)	513 (31)*	150 (28)**	.002
CPAP in the DR, n (%)	314 (34)	588 (36)	194 (36)	.74
Intubation in the NICU within the first 4 h after admission to the unit, n (%)	43 (5)	82 (5)	28 (5)	.84
Intubation during the first 24 h of life, n (%)	220 (23)	242 (15)**	75 (14)**	<.001
Surfactant, n (%)	105 (11)	131 (8)*	50 (9)	.01
Pneumothorax, n (%)	29 (3)	40 (2)	12 (2)	.51
Death before discharge, n (%)	17 (2)	19 (1)	8 (2)	.41
Chronic lung disease, n (%)	31 (3)	40 (2)	16 (3)	.44
Total no. days intubated (endotracheal tube or tracheostomy) (n = 694); median (quartiles) <sup>b</sup>	1 (1–3)	1 (0–4)	1 (1–6)	.097
Patent ductus arteriosus, n (%)	68 (7)	106 (6)	23 (4)	.07
Necrotizing enterocolitis, stage ≥2, n (%)	17 (2)	23 (1)	12 (2)	.42
Intraventricular hemorrhage, grade 3 or 4, n (%)	8 (0.8)	7 (0.4)	5 (0.9)	.22
Periventricular leukomalacia, n (%)	3 (0.3)	13 (0.8)	4 (0.7)	.323
Retinopathy of prematurity, stage ≥3, n (%)	3 (0.3)	0 (0)	3 (0.5)	.008

P values in the last column on the right are based on  $\chi^2$  analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined by using  $P < .025$ , and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

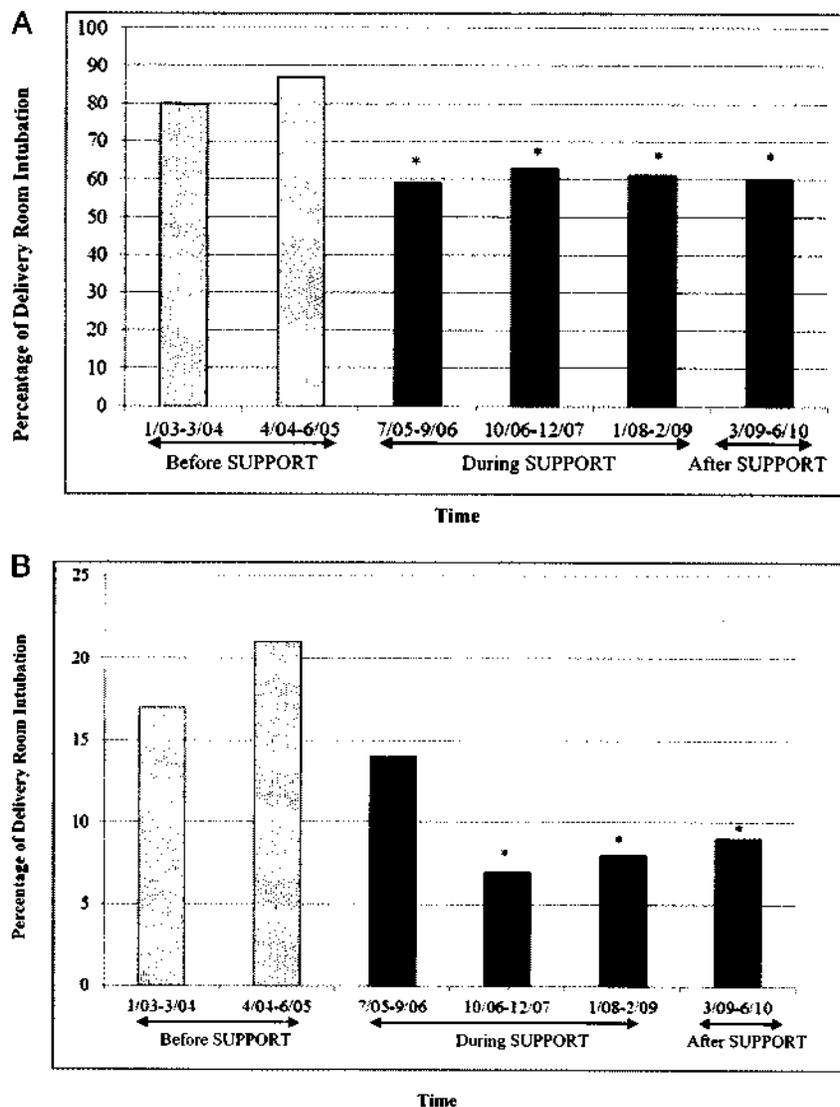
<sup>a</sup> In the upper GA group, 95% of data were available, we used the total number available as denominator.

<sup>b</sup> Kruskal-Wallis tests.

more mature patients soon after SUPPORT initiation and persisted through 16 months of posttrial evaluation. This change in practice at PMH was much larger than in other comparable centers that did not participate in any trial involving random allocation to DR intubation, suggesting that the trial participation itself influenced clinical practice well beyond the study participants.

PMH is a high-volume delivery unit with 12 000 to 15 000 deliveries per year. At PMH, the decision whether to intubate is made by resuscitation teams of practitioners who are trained in the neonatal resuscitation program. Teams for neonates with GA of 30 to 35 weeks include a nurse, a respiratory therapist, and a neonatal nurse practitioner or a senior pediatric resident. Teams for lower GA neonates also include a neonatal-perinatal fellow. Additional personnel are available for backup. The same teams provided care to all neonates, whether enrolled into SUPPORT or not. PMH did not have a policy about DR endotracheal intubation; decisions are left to team leaders according to national guidelines for neonatal resuscitation. At PMH before SUPPORT, most preterm neonates <28 weeks' GA were intubated in the DR. PMH did not participate in the NRN Feasibility Trial,<sup>13</sup> which preceded SUPPORT. At PMH, the only evident change in DR management was initiation of a resuscitation rotation for fellows in neonatal-perinatal medicine in 2005. The Neonatal Resuscitation Program mentioned the use of CPAP in the DR for preterm neonates in 2006, and included CPAP in the resuscitation algorithm in 2010<sup>31,32</sup>; however, immediate application of CPAP in the DR at PMH was not recommended for all preterm neonates <32 weeks until May 1, 2011.

The strengths of the current study include<sup>33,34</sup> large sample size; prospective validated databases thereby



**FIGURE 2**

Analysis of temporal patterns in DR intubation rates by GA group at PMH. This analysis was performed using consecutive 15- to 16-month blocks. A, Lower GA group (24<sup>0/7</sup>–27<sup>6/7</sup> weeks' GA infants): The percentages of DR intubation were not significantly different between blocks before SUPPORT ( $P = .37$ ); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into the SUPPORT ( $P < .001$ ). This change already occurred within the first 15 months of recruitment into SUPPORT. \*Indicates significant (with Bonferroni adjustment,  $P < .0125$ ) pairwise difference from baseline before starting the SUPPORT. B, Upper GA group (28<sup>0/7</sup>–34<sup>6/7</sup> weeks' GA infants). The percentage of DR intubations was not significantly different between the 2 blocks before SUPPORT ( $P = .10$ ); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into SUPPORT ( $P < .001$ ); however, this change started to reach significance only after 15 months of recruitment into SUPPORT. \*Indicates significant (with Bonferroni adjustment,  $P < .0125$ ) pairwise difference from baseline before starting SUPPORT.

comparable centers. It is unlikely that the current study affected the proportion of DR intubation because when the first data were obtained and presented at a national meeting, the change in practice had already taken place. We did not observe a regression to the mean but instead a sustained reduction in DR intubation at PMH during/after SUPPORT. A differential Hawthorne effect was ruled out because providers were not aware of an observational study of eligible, non-enrolled patients during SUPPORT.<sup>7,8</sup> This study was limited to a single institution rather than all NRN centers participating in SUPPORT because the generic database of the NRN includes only the most immature infants; patients in the upper GA group were important in this study as positive controls who were not eligible for SUPPORT and thus not subjected to selection bias. Selection bias at PMH in the lower GA group during SUPPORT is unlikely to explain the observed decrease in DR intubation in nonenrolled patients, because respiratory distress is associated with lower exposure to antenatal steroids,<sup>35</sup> and more frequent DR positive pressure ventilation (Appendix) would be expected to increase, rather than decrease, DR intubation. The lower percentage of antenatal steroids among nonenrolled patients could have resulted because of many reasons, including not enough time before delivery.<sup>7</sup> Rich and colleagues' study showed that a significantly larger proportion of eligible infants whose mothers were not approached for consent to SUPPORT had no prenatal steroid exposure. The frequency of antenatal corticosteroid administration at PMH is low because preeclampsia and diabetes are considered contraindications.<sup>36</sup> Multivariate analyses showed that the RR of DR intubation decreased at PMH and decreased more at PMH than in VON, even taking into account antenatal

minimizing missing data, information bias, and loss to follow-up; stratified analysis yielding internal controls (upper GA group); and multivariate comparison with contemporaneous external controls (comparable VON

centers not participating in DR trials) with a similar baseline proportion of DR intubation. Secular trends are unlikely to explain the primary results because DR intubation at PMH decreased much more than in other

**TABLE 7** Adjusted RR Estimates in Preterm Infants Born With GA 24 to 29<sup>6/7</sup> Weeks at PMH and in Comparable North American Centers in the VON Before SUPPORT (2003–2004) and During/After SUPPORT (2006–2009)

Care Process	GA Group, wk	Location	Before SUPPORT	During/After SUPPORT	Adjusted RR* During/After Versus Before SUPPORT (95% CI)	Ratio of RRs PMH Versus VON (95% CI)	P Value
Intubated in DR	24 <sup>0/7</sup> –27 <sup>6/7</sup>	PMH	105/128 (82%)	99/164 (60%)	0.745 (0.644–0.861)	0.757 (0.654–0.875)	.0002
		VON	11 728/13726 (85.4%)	29 715/35 447 (83.8%)	0.984 (0.976–0.992) <i>n</i> = 49 055		
	28 <sup>0/7</sup> –29 <sup>6/7</sup>	PMH	51/86 (59%)	57/198 (29.0%)	0.495 (0.375–0.652)	0.516 (0.391–0.681)	< .0001
		VON	5427/10 008 (54.2%)	13 457/25 928 (51.9%)	0.959 (0.939–0.979) <i>n</i> = 35 851		
Received any invasive ventilation	24 <sup>0/7</sup> –27 <sup>6/7</sup>	PMH	119/128 (93.0%)	144/164 (88.0%)	0.952 (0.886–1.023)	0.965 (0.898–1.037)	.33
		VON	13 158/13 727 (95.9%)	33 469/35 453 (94.4%)	0.986 (0.982–0.991) <i>n</i> = 49 068		
	28 <sup>0/7</sup> –29 <sup>6/7</sup>	PMH	63/86 (73.0%)	134/198 (68.0%)	0.939 (0.804–1.095)	0.988 (0.846–1.154)	.88
		VON	7599/10 008 (75.9%)	18 669/25 930 (72.0%)	0.950 (0.937–0.962) <i>n</i> = 35 855		

\*RR estimates are adjusted for infants' GA, gender, z-score for BW (computed within GA and gender), and exposure to antenatal corticosteroids by using robust Poisson regression generalized estimating equation models. Location (PMH and VON) and time period (during/after SUPPORT and before SUPPORT) were represented by a 4-level categorical variable. RRs and the ratio of RR estimates were computed based on the appropriate linear contrast of model parameters.

corticosteroid administration. We were unable to analyze bronchopulmonary dysplasia, or other elements of care process examined in SUPPORT (ie, targeted ventilation strategy and oxygen saturation), which were not included in the PMH databases. In addition, target oxygen saturation values of 88% to 94%, a PMH NICU policy since May 2002,<sup>37</sup> was used for nonenrolled patients. Because the study used databases, it was not possible to perform a propensity match, or a cluster analysis of DR team members or individual providers and to obtain their rationale for deciding whether to intubate the trachea. It is possible that the change in DR intubation was related to increased availability of T-piece devices for DR resuscitation, or to training and experience with these devices and DR CPAP.

## CONCLUSIONS

A change in process of care was observed in nonenrolled patients during/after recruitment to an unblinded RCT, in the absence of changes in standard care, initiation of a protocol, or previously described trial effect. This suggests that care for patients who are not enrolled in RCTs should routinely be

monitored and audited to identify changes in practice that may either be beneficial or detrimental without the evidence from a completed trial. Further studies are needed to investigate the determinants of changes in individual decisions about care process (eg, observations of short-term outcomes versus experience with novel processes of care). A trial design in which centers are randomized to participation in RCTs could further analyze the impact of changes in care process associated with unblinded RCTs.

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The first version of the PMH cohort was a poster presentation at the Pediatric Academy Society Meeting, Honolulu, HI, May 4, 2008: Brion LP, Wyckoff MH, Jaleel M, Sanchez PJ, Burchfield J, Christie L. Delivery room practice change following the initiation of the SUPPORT trial.

The final version of the PMH cohort was a platform presentation at the Pediatric Academy Society Meeting, Boston, MA, April 28, 2012: LeVan JM, Wyckoff MH, Jaleel MA, Sanchez PJ, Ahn C, Burchfield J, Christie L, Brion LP. Impact of initiating the NICHD Neonatal Research Network SUPPORT Trial on management and out-

comes of gestational-age matched non-enrolled patients.

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(Continued from first page)

This trial has been registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier NCT01601886).

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**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**APPENDIX** Baseline Characteristics of Infants 24 to 27<sup>6/7</sup> Weeks' Gestation Born at PMH During SUPPORT (July 2005–February 2009)

Q:11	Characteristic	SUPPORT, n = 73, Excluded From the Current Study	NONSUPPORT, n = 132, Included in the Current Study	P Value
	GA, wk, mean (SD)	25.3 (1.0)	25.9 (1.0)	<.001
	BW, g, mean (SD)	878 (189)	907 (238)	.37
	Size for age, n (%)			.03
	Small for GA	1 (1)	14 (11)	
	Large for GA	19 (26)	25 (19)	
	Female, n (%)	29 (40)	61 (46)	.23
	Multiple birth, n (%)	12 (16)	19 (14)	.69
	Use of antenatal steroids, n (%)	49 (67)	52 (39)	<.001
	Abruptio placentae, n (%)	3 (4)	11 (8)	.39
	Placenta previa, n (%)	1 (1)	1 (1)	1.00
	Maternal diabetes, n (%)	6 (8)	10 (8)	1.00
	Gestational hypertension or preeclampsia, n (%)	15 (21)	28 (21)	1.00
	Clinic attendance, n (%)	63 (86)	113 (86)	1.00
	Positive pressure ventilation in the DR, n (%)	42 (58)	106 (80)	.001

Significance based on Fisher's exact tests or Student's *t* tests.

## AUTHOR QUERIES

### **AUTHOR PLEASE ANSWER ALL QUERIES**

- 1—Titles are limited to 2 lines of printed text; if your title goes beyond this limit, please reduce the length to no more than 97 characters (including spaces and punctuation). No change needed
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- 7—Sentence beginning "Rich and colleagues' study showed that a significantly...": Please indicate which Rich reference you are citing here. Reference 7
- 8—Please include a reference for "the study by Rich and collaborators." Also, please verify that all information included in the Acknowledgments section should be there. References 7 and 8
- 9—All dots that resemble multiplication dots have been changed to decimal points throughout. Please verify. OK
- 10—Tables 1A, 1B, 2A, 2B, 3A, and 3B have been renumbered as Tables 1 to 6 per journal style. Please verify all edits to table titles and footnotes. Changes made in the the table
- 11—*P* values theoretically should never reach 1.00. Please change all 1.00 *P* values to their prerounded values. p=1.000 (SPSS gives p value with 3 decimals)

**From:** [Stile, Christina \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Rowe, Mona \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Clearance | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT  
**Date:** Wednesday, December 04, 2013 8:26:21 AM

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i will work to get it cleared out of the system. thanks—c

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, December 04, 2013 7:59 AM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Stile, Christina (NIH/NICHD) [E]  
**Subject:** RE: Clearance | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Thanks, Mona. I have this sentence in my template now for all NRN papers. Whether it appears in the print versions once published is somewhat up to the editors, but I can try to check for it when I see proofs (which doesn't always happen).

How do we get this out of the online Clearance System? It is still listed in my queue as "PICB Admin Triage." Does Cathy need to clear it again or is this for someone else?

Stephanie

---

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---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Tuesday, December 03, 2013 4:14 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Stile, Christina (NIH/NICHD) [E]  
**Subject:** RE: Clearance | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Hi Stephanie and Rose – this came through Track 1 –so we do not see it up here through the system –only track2s make it to me automatically through the clearance system. There are no clinical treatment findings that suggest something one way or another so I don't really see a (b)(5)

(b)(5)

However, the sentence that Stephanie shared earlier may be (b)(5)  
.. "While NICHD staff did have input into the study design, conduct, analysis, and manuscript drafting, the comments and views of the authors do not necessarily represent the views of the NICHD." It may be good practice to (b)(5)

(b)(5)

Thoughts?

*Mona*

Mona Jaffe Rowe, M.C.P.  
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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, December 03, 2013 11:03 AM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Clearance | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Hi Mona,

Can you tell us what the status is for NICHD Clearance on Namazivayam Ambalavan's SUPPORT paper, "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)"? It was submitted back in September; he is ready to send it to the journal now.

Thank you,

Stephanie

---

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, December 03, 2013 10:56 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Hi Stephanie,

Did this manuscript go through NICHD clearance already? It has been through the publication subcommittee. If not, I will send a revised version for clearance.

Ambal

---

**From:** Namasivayam Ambalavanan  
**Sent:** Friday, August 30, 2013 2:30 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Namasivayam Ambalavanan; Wally Carlo, M.D.  
**Subject:** RE: Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Hi Stephanie,

There were only a few minor comments on the previous draft. I think we can now send it to the Publication subcommittee for review. Would you be able to forward it to them (maybe next Tuesday, as it is already late on Friday before a long weekend)?

Thanks,

Ambal

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**Cc:** Namasivayam Ambalavanan

**Subject:** Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Ambal is planning on submitting his paper, "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" to Pediatrics.

This journal is now requiring that the corresponding author "certify that all persons named in the acknowledgment section have provided me with written permission to be named." We have gathered blanket agreements from most people on the boilerplate in the past; however, we still need agreements from those highlighted in yellow in the attached boilerplate. These do NOT need to have a signature on them if the person can email their agreement to me.

NOTE: Since many of the highlighted names are for FU examiners, I have copied the FU PIs here for their assistance.

Please send an **Acknowledgement Agreement** (form attached) for each person to me at [archerst@mail.nih.gov](mailto:archerst@mail.nih.gov) by **Friday, August 23<sup>rd</sup>**.

**If we do not have a person's agreement by the time we receive proofs, we will delete that person from the acknowledgements.**

Thank you,

Stephanie Archer

---

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT  
**Date:** Tuesday, December 03, 2013 10:58:40 AM

---

Send her an email

Thanks

Rose

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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, December 03, 2013 10:58 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Did you hear back from Mona about this? Or should I call her?

---

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, December 03, 2013 10:56 AM  
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**Subject:** RE: Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

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Ambal

---

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Ambal

Namasivayam Ambalavanan MD  
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Professor, Departments of Pediatrics, Molecular and Cellular Pathology, and Cell, Developmental, and Integrative Biology  
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**From:** Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]  
**Sent:** Friday, August 09, 2013 3:16 PM  
**To:** Abbot Laptook ([alaptook@WIHRI.org](mailto:alaptook@WIHRI.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Barbara Stoll ([barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu)); Brenda Poindexter ([bpindex@iupui.edu](mailto:bpindex@iupui.edu)); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); Ed Donovan ([edward.donovan@cchmc.org](mailto:edward.donovan@cchmc.org)); Ivan Frantz ([IFrantz@tufts-nemc.org](mailto:IFrantz@tufts-nemc.org)); Kathleen Kennedy ([Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)); Krisa P. Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); Kurt Schibler ([kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)); Michele C. Walsh ([mcw3@cwru.edu](mailto:mcw3@cwru.edu)); Pablo Sanchez ([Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu)); Richard Ehrenkranz ([richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)); Roger G. Faix ([roger.faix@hsc.utah.edu](mailto:roger.faix@hsc.utah.edu)); Ron Goldberg ([goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu)); Seetha Shankaran ([sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu)); Wally Carlo, M.D.; Av Fanaroff ([aaf2@cwru.edu](mailto:aaf2@cwru.edu)); Charles Bauer ([cbauer@pediatrics.med.miami.edu](mailto:cbauer@pediatrics.med.miami.edu)); Dale L. Phelps ([dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)); Michael O' Shea ([moshea@wfubmc.edu](mailto:moshea@wfubmc.edu)); Neil Finer ([nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)); Shahnaz Duara ([sduara@miami.edu](mailto:sduara@miami.edu)); Athina Pappas ([apappas@med.wayne.edu](mailto:apappas@med.wayne.edu)); Betty Vohr ([bvohr@wihri.org](mailto:bvohr@wihri.org)); Carolyn Petrie Huitema ([petrie@rti.org](mailto:petrie@rti.org)); Dee Wilson ([drficmd@aol.com](mailto:drficmd@aol.com)); Diane Marshall ([diane\\_marshall@med.unc.edu](mailto:diane_marshall@med.unc.edu)); Elisabeth McGowan ([EMcGowan@tufts-nemc.org](mailto:EMcGowan@tufts-nemc.org)); Gary Myers ([gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu)); Hallam Hurt ([hurt@email.chop.edu](mailto:hurt@email.chop.edu)); Howard Kilbride ([hkilbride@cmh.edu](mailto:hkilbride@cmh.edu)); Ira Adams-Chapman ([iadamsc@emory.edu](mailto:iadamsc@emory.edu)); Isabel Purdy ([ipurdy@mednet.ucla.edu](mailto:ipurdy@mednet.ucla.edu)); Jamie Newman ([newman@rti.org](mailto:newman@rti.org)); Janell Fuller ([JaFuller@salud.unm.edu](mailto:JaFuller@salud.unm.edu)); Jenna Gabrio ([jgabrio@rti.org](mailto:jgabrio@rti.org)); Keith Yeates ([Keith.Yeates@nationwidechildrens.org](mailto:Keith.Yeates@nationwidechildrens.org)); Kim Yolton ([Kimberly.Yolton@cchmc.org](mailto:Kimberly.Yolton@cchmc.org)); Kristin Zaterka-Baxter ([kzaterka@rti.org](mailto:kzaterka@rti.org)); Marsha Gerdes ([gerdes@email.chop.edu](mailto:gerdes@email.chop.edu)); Meg Cunningham ([mcunningham@rti.org](mailto:mcunningham@rti.org)); Myriam Peralta, M.D.; Patricia

Evans ([Patricia.W.Evans@uth.tmc.edu](mailto:Patricia.W.Evans@uth.tmc.edu)); Rachele Tyler ([rt Tyler@mednet.ucla.edu](mailto:rt Tyler@mednet.ucla.edu)); Ricki Goldstein ([gold5005@mc.duke.edu](mailto:gold5005@mc.duke.edu)); Roy Heyne ([Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu)); Soraya Abbasi ([soraya.abbasi@uphs.upenn.edu](mailto:soraya.abbasi@uphs.upenn.edu)); Susan Hintz ([srhintz@stanford.edu](mailto:srhintz@stanford.edu)); Tarah Colaizy ([tarah-colaizy@uiowa.edu](mailto:tarah-colaizy@uiowa.edu)); Yvonne Vaucher ([yvaucher@ucsd.edu](mailto:yvaucher@ucsd.edu))

**Cc:** Namasivayam Ambalavanan

**Subject:** Acknowledgement Agreements | Ambalavanan, Association of PaCO2 with outcomes in the SUPPORT

Ambal is planning on submitting his paper, "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" to Pediatrics.

This journal is now requiring that the corresponding author "certify that all persons named in the acknowledgment section have provided me with written permission to be named." We have gathered blanket agreements from most people on the boilerplate in the past; however, we still need agreements from those highlighted in yellow in the attached boilerplate. These do NOT need to have a signature on them if the person can email their agreement to me.

NOTE: Since many of the highlighted names are for FU examiners, I have copied the FU PIs here for their assistance.

Please send an **Acknowledgement Agreement** (form attached) for each person to me at [archerst@mail.nih.gov](mailto:archerst@mail.nih.gov) by **Friday, August 23<sup>rd</sup>**.

**If we do not have a person's agreement by the time we receive proofs, we will delete that person from the acknowledgements.**

Thank you,

Stephanie Archer

---

Stephanie Wilson Archer

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Pregnancy & Perinatology Branch

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[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

**From:** [Finer, Neil](#)  
**To:** [Wally Carlo, M.D.](#); [Gantz, Marie](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: Hot Topics  
**Date:** Monday, December 02, 2013 11:43:35 PM

---

These data are very similar  
I look forward to your presentation Wally  
Neil

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, December 02, 2013 10:30 PM  
**To:** Gantz, Marie  
**Cc:** Rosemary Higgins; Finer, Neil  
**Subject:** Re: Hot Topics

Marie.

I wanted to present it at hot topics. I probably can use the one you already did.

Can you send it to me?

Rose.

I would need SC approval to present it. Can you request that ?

Wally

Sent from my iPhone

On Dec 2, 2013, at 4:13 PM, "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)> wrote:

Hi all,

Today is my first day back from (b)(6) and I wanted to follow up to see what needs to be done for the analysis proposed below and what the timeline is. From graphs I have produced previously, our data look very similar to Figure 1 of the BOOST II paper when similar graphing methods are used.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-597-5110

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, October 28, 2013 1:25 PM

**To:** Rosemary Higgins; Finer, Neil; Gantz, Marie  
**Subject:** FW: Hot Topics

Hi Rose, Neil, and Marie:

One of the concerns of how we reported O2 sat distribution in SUPPORT is that we used median sat per baby rather than % of time at each oxygen saturation.

Enclosed is the BOOST II paper. See how they reported their O2 sat data on Figure 1. Can we get our analysis done that way for Hot Topics? Ben thinks we could compare better O2 separation that way.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: (b)(6)

---

**From:** Stenson, Ben [mailto:Ben.Stenson@nhslothian.scot.nhs.uk]  
**Sent:** Monday, October 28, 2013 12:19 PM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: Hot Topics

Yes.

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** 28 October 2013 17:17  
**To:** Stenson, Ben  
**Subject:** RE: Hot Topics

Hi Ben:

Do you mean to report it as you did in your Fig 1 with average % of time spent by infants at each saturation?

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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---

**From:** Stenson, Ben [<mailto:Ben.Stenson@nhslothian.scot.nhs.uk>]  
**Sent:** Monday, October 28, 2013 11:59 AM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: Hot Topics

Hi Wally

It appears that there are still important differences of view about the effect of the different oximeters on saturation. Did you find out whether you would be able to show the saturation distributions of your Support babies in the same way that was done in BOOST as well as in the way that you did in the support paper so that there is a comparison that goes beyond the median sats histograms?

Ben

\*\*\*\*\*

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\*\*\*\*\*

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, November 27, 2013 3:53 PM  
**To:** Maddox, Yvonne (NIH/NIMHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]

<http://www.clinicaltrials.gov/ct2/show/NCT01192776?term=hypothermia+infant&rank=41>

NCT01192776

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Wednesday, November 27, 2013 3:08 PM  
**To:** Maddox, Yvonne (NIH/NIMHD) [E]; Stephan, Kathleen (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Rose and Cathy contact phone #s

Rose's cell (b)(6)  
Rose's home (b)(6)  
Rose's office 301 435 7909

Cathy's cell (b)(6)  
Cathy's home (b)(6)  
Cathy's office 301 435 6894

Catherine Y. Spong, MD  
Director, Division of Extramural Research  
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Email: [spong@c@mail.nih.gov](mailto:spong@c@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Boghossian, Nansi (NIH/NICHD) [E]  
**Cc:** srhintz@stanford.edu  
**Subject:** FW: potential SUPPORT proposal  
**Date:** Wednesday, November 27, 2013 10:08:31 AM  
**Attachments:** ANS+later mental health - PLOSOne 2013.pdf

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Nansi

You would need to discuss with Dr. Susan Hintz, the study PI, and partner with an NRN site. I know that many of the items already have pre-defined secondary analyses and authors selected.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Boghossian, Nansi (NIH/NICHD) [F]  
**Sent:** Wednesday, November 27, 2013 10:05 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** potential SUPPORT proposal

Dear Rose,

The attached article just came out. The authors showed that prenatal synthetic glucocorticoids were significantly associated with general psychiatric disturbance and inattention at 8 years. The authors claim that the glucocorticoids have a programming effect on the fetal brain. The study used data from the Northern Finland Birth Cohort 1986 but the sample size was very small limited to 37 infants exposed to glucocorticoids and 185 controls.

To follow-up on this finding, we are suggesting to (b)(5)  
(b)(5) I looked at the (b)(5)  
(b)(5) So we are thinking of (b)(5)  
(b)(5) Please let us know if this is a good plan to proceed with.

Thanks  
nansi

# Prenatal Glucocorticoid Treatment and Later Mental Health in Children and Adolescents

Natasha Khalife<sup>1</sup>, Vivette Glover<sup>2</sup>, Anja Taanila<sup>3,4</sup>, Hanna Ebeling<sup>5,6</sup>, Marjo-Riitta Järvelin<sup>1,3,7,8,9,10</sup>, Alina Rodriguez<sup>1,11</sup>\*

**1** Department of Epidemiology and Biostatistics, Imperial College London, London, United Kingdom, **2** Institute of Reproductive and Developmental Biology, Imperial College London, London, United Kingdom, **3** Institute of Health Sciences, University of Oulu, Oulu, Finland, **4** Unit of General Practice, Oulu University Hospital, Oulu, Finland, **5** Institute of Clinical Medicine, Clinic of Child Psychiatry, University of Oulu, Oulu, Finland, **6** Clinic of Child Psychiatry, Oulu University Hospital, Oulu, Finland, **7** Unit of Primary Care, Oulu University Hospital, Oulu, Finland, **8** MRC Health Protection Agency (HPA) Centre for Environment and Health, Imperial College London, London, United Kingdom, **9** Department of Children and Young People and Families, National Institute for Health and Welfare, Oulu, Finland, **10** Biocenter Oulu, University of Oulu, Oulu, Finland, **11** Department of Psychology, Mid Sweden University, Östersund, Sweden

## Abstract

**Background:** Animal studies demonstrate a clear link between prenatal exposure to glucocorticoids (GC) and altered offspring brain development. We aim to examine whether prenatal GC exposure programs long-term mental health in humans.

**Methods:** Using propensity-score-matching, children prenatally exposed to synthetic glucocorticoids (sGC),  $n=37$ , and controls,  $n=185$ , were balanced on important confounders related to sGC treatment – gestational age and pre-pregnancy BMI. We also used mixed-effects modeling to analyse the entire cohort – matching each sGC case,  $n=37$ , to all possible controls,  $n=6079$ , on gestational age and sex. We obtained data from the Northern Finland Birth Cohort 1986 at four waves – pregnancy, birth, 8 and 16 years. Data on pregnancy and birth outcomes came from medical records. Mental health was assessed at 8 years by teachers with the Rutter B2 scale, and at 16 years by parents with the Strengths and Weaknesses of ADHD symptoms and Normal behavior (SWAN) scale and adolescents by the Youth Self-Report (YSR) scale.

**Results:** Prenatal sGC treatment was consistently associated with adverse mental health in childhood and adolescence, as shown by both the propensity-score method and mixed-effects model. Using the propensity-score-matched subsample, linear multiple regression showed prenatal sGC was significantly linked with general psychiatric disturbance ( $B=8.34$  [95% CI: 2.3–16.45]) and inattention ( $B=.97$  [95% CI: .16–1.80]) at 8 years after control for relevant confounders. Similar findings were obtained at 16 years, but did not reach statistical significance. Mediation by birthweight/placental weight was not detected.

**Conclusions:** This study is the first to prospectively investigate the long-term associations between prenatal exposure to sGC treatment and mental health in children and adolescents. We report an association between prenatal exposure to sGC and child mental health, supportive of the idea that sGC has a programming effect on the fetal brain.

**Citation:** Khalife N, Glover V, Taanila A, Ebeling H, Järvelin M-R, et al. (2013) Prenatal Glucocorticoid Treatment and Later Mental Health in Children and Adolescents. PLoS ONE 8(11): e81394. doi:10.1371/journal.pone.0081394

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**Competing Interests:** The authors have declared that no competing interests exist.

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## Introduction

Cortisol, a naturally occurring glucocorticoid (GC), plays a vital role in fetal development [1]. This hormone exerts a wide range of effects in most regions of the developing brain, initiating terminal maturation, remodeling of axons and

dendrites, and affecting cell survival [2]. However, sustained elevation or reduction of GC levels can impair these processes, and thereby permanently modify brain structure and function [3], suggesting a role for GC in fetal programming of mental health. Fetal exposure to elevated levels of maternal cortisol has been proposed as one mechanism underlying the reported

connection between prenatal exposure to maternal stress and symptoms of attention-deficit/hyperactivity disorder (ADHD) in the offspring [4-6]. ADHD is the most common behavioral disorder in young people, characterized by inappropriate inattention, hyperactivity and impulsivity [7,8], and is related to impairments in all areas of life e.g. social and scholastic domains [9].

Animal models provide strong evidence that prenatal exposure to both elevated endogenous maternal GC and synthetic glucocorticoids (sGC) alter fetal brain development and consequently impact upon behavior [6,10,11], including hyperactivity [12] and attention [13]. However, without experimental evidence in humans the effect cannot be confirmed. The routine administration of sGC in cases of threatened pre-term birth offers an opportunity to study whether prenatal exposure to GC is associated with long-term programming of behavior in humans in a quasi-experimental manner.

sGC is commonly administered to pregnant women when pre-term birth is impending to accelerate fetal lung maturation and thereby reduce the risk of respiratory distress syndrome, and neonatal mortality [14]. Yet, very little is known about the long-term effects of prenatal sGC treatment on child behavior, including ADHD symptoms. The few existing studies report inconsistent findings. Some studies report an association between repeated prenatal sGC treatment and distractibility, hyperactivity and aggressive behavior [15], as well as attention problems [16] in young children, but others do not [17-19]. Generally, studies are limited by short follow-up times (young children only) and mostly examine the impact of repeated doses of prenatal sGC, and so little is known about the long-term impact of low/infrequent doses of prenatal sGC exposure on later child behavior. This is particularly important given that current guidelines recommend that only a single course of sGC should be administered (either 2 doses of 12mg of betamethasone or 4 doses of 6mg of dexamethasone) because of concerns regarding potential long-term effects of repeated sGC treatment [20]. One study examined the long-term association and reported that adults at age 31 who received a single course of prenatal sGC did not differ on mental health outcomes from those in the placebo condition [21]. However, the placebo group in this study received cortisone acetate with a 70<sup>th</sup> of sGC potency, and so the impact of sGC from non-exposure cannot be completely assessed. Further studies are thus needed to examine this association.

Besides the potential impact on the fetal brain, prenatal exposure to sGC treatment in humans has been linked with reduced birth size [22]. Small size at birth, in turn, has been implicated as a risk factor for child mental health [23]. It is possible that small birth size, which is a marker of suboptimal intrauterine conditions, may reflect altered brain development [23]. Prenatal exposure to maternal stress has also been linked to reduced birth size [24], with excess maternal GC as a potential causal mechanism [6]. The placenta, which normally acts as a barrier to regulate fetal exposure to endogenous maternal GC (inactivating excess cortisol to cortisone) [25], may play a key role in GC programming [26]. Prenatal exposure to sGC and maternal stress have also been

associated with altered placental size [27,28], which in turn has been linked with child and adolescent mental health [29]. Changes in placental size can affect fetal nutrient and hormone supply [30], resulting in altered fetal growth and organ development, including the brain. Thus, it is possible that the GC-mental health link is mediated by deviation in either birth size and/or placental size.

To clarify previous inconsistent findings, we examined data from a large, longitudinal cohort following children and adolescents. In studies examining prenatal sGC effects on child mental health, treatment-selection bias is a main issue, which we address here. It is essential to disentangle the potential effect of treatment from the conditions precipitating treatment. Our large dataset enabled us to very accurately match prenatally sGC exposed (cases) and unexposed (controls) children on baseline characteristics related to sGC treatment, by means of propensity-score-matching. However, an important limitation of propensity-score-matching is that, particularly in large studies, many unmatched controls are excluded from analysis, resulting in loss of data which may reduce the precision of the estimated association between the treatment and outcome [31]. Thus, we also used the entire cohort to analyse the data – matching each case to all possible controls on important confounders. The two matching procedures allowed us firstly to isolate the impact of prenatal sGC exposure on mental health from the confounding effects of treatment, and secondly, to examine the robustness of the results, thereby addressing important limitations of previous research. Further, we investigated whether birthweight and placental weight mediate the association between prenatal sGC treatment and offspring mental health to gain insight into the potential causal pathway. This is the first study to investigate the long-term impact of prenatal sGC treatment (low/infrequent doses) versus no treatment on mental health, particularly ADHD symptoms, in childhood (8 years) and again in adolescence (16 years). We hypothesise that prenatal sGC treatment will be related to poor mental health outcomes.

## Materials and Methods

### Participants

The Northern Finland Birth Cohort (NFBC) 1986 recruited women in early pregnancy with an expected date of delivery between July 1, 1985 to June 30, 1986; 99% participated. Prospective data was gathered from pregnancy to child age 16 years. The cohort consists of 9479 births in Oulu and Lapland provinces. Here, we include N=8954 liveborn singletons with consent to use their data (exclusions: 226 twins, 6 triplets and 249 without consent).

All pregnant women, literate in Finnish, were consecutively recruited at their first prenatal health care visit to tax-paid prenatal health services, which offer high-quality standardized care used by essentially all women in the country [32]. Women provided information via structured self-report questionnaires. Antenatal clinical and birth outcome data were obtained from maternity health centres and hospital medical records (completed by midwives during pregnancy and at birth), and abstracted onto study forms. As the original NFBC 1986

dataset did not include data on prenatal sGC treatment. We screened for potential sGC cases by performing a systematic chart review (see Figure S1).

The cohort was followed-up at child ages 8 years ( $n=8106$ ; 91% of original sample) and 16 years ( $n=6934$ ; 77% of original sample), and focused on child health and well-being. Follow-ups were carried out using the national population-based registries, which identify all residents by unique personal numbers, to obtain current addresses. Thus, participants could be traced even outside the original geographic area.

The ethics committee of Northern Ostrobothnia Hospital District approved the study, and both parents and adolescents gave written informed consent.

### Predictor: Prenatal sGC Treatment

In Finland in 1985/86, prenatal sGC treatment was administered in rare cases (at the discretion of the medical practitioner) as use of sGC during pregnancy was still controversial at the time, which explains the relatively few number of sGC cases in our study. There was no standard protocol for sGC treatment in the NFBC 1986 cohort, although caution was taken as only small and infrequent doses were administered. Dexamethasone ( $n=33$ ) or betamethasone ( $n=4$ ) - the drugs of choice for threatened pre-term birth, were administered. At 8 and 16 years,  $n=37$  and  $n=29$  cases respectively were available for analysis. Out of the 37 cases (at 8 years), 13 received a single sGC dose, 23 received 2 doses and the dose number for 1 case was not recorded. The total dosage ranged from 10mg to 25mg (the maximum total dosage equates approximately to a single course of sGC treatment as recommended by current guidelines). We obtained data on sGC treatment, number of sGC doses, total sGC dose and the interval between prenatal sGC exposure and birth (days), from medical records.

Fetal exposure to GC is regulated by placental 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2) - an enzyme which normally inactivates 50-90% of endogenous maternal GC [25,33], but does not extensively metabolize sGC. Placental 11 $\beta$ -HSD2 inactivates only about 2% of dexamethasone and 7% of betamethasone [34], allowing the majority of sGC to cross the placenta to exert its intended therapeutic effect on fetal tissues. In contrast, prednisone ( $n=2$ ) and hydrocortisone ( $n=1$ ) have minimal placental transfer and so are typically administered to treat maternal medical conditions (e.g. allergic or inflammatory diseases) and were excluded from the analyses.

Betamethasone and dexamethasone are long-acting substances (with biological half-lives ranging between 36 and 54 hours) [35], so it is unlikely that sGC treatment close to the time of birth could significantly impact fetal brain development as there would not be sufficient time for the drug to induce maximum effect. Thus, we excluded cases who had been exposed to sGC  $\leq 4$  days prior birth ( $n=11$ ).

### Potential Mediators: Birthweight and Placental Weight

Birthweight (grams) was measured accurate to  $\pm 10g$ , immediately after birth by medical personnel. Placentas were washed with water and then weighed (including membranes

and umbilical cord, cut approximately 5cm from the neonate) to the nearest gram within 30 minutes after birth, according to standard protocols [29].

### Outcome: Child and Adolescent Mental health

Teachers assessed child behavior at the age of 8 years using the Rutter B2 scale [36], a well-validated screener for childhood mental health. Each of the 26 items is rated as either 'certainly applies' (scored 2), 'applies somewhat' (scored 1) or 'does not apply' (scored 0); yielding a total score between 0 to 52. The questionnaire generates three sub-scores: neurotic, antisocial and inattention-hyperactivity. Additionally, we examined the core ADHD symptoms individually i.e. inattention and hyperactivity.

Parents reported adolescent behavior at 16 years using the Strengths and Weaknesses of ADHD symptoms and Normal behavior (SWAN) scale [37]. The SWAN consists of 18 items based on the symptoms of ADHD listed in the DSM-IV (9 items in the inattention subscale, 9 items in the hyperactive-impulsivity subscale, and together the 18 items indicate ADHD combined subtype). As this scale measures both weaknesses (scored 3, 2, 1) and strengths (scored -1, -2, -3), along with average behavior (scored 0), it is expected to produce a normal distribution of behavioral scores, thereby reducing the risk of over/under identifying ADHD behavior.

Adolescents provided mental health self-reports at 16 years by completing the Youth Self-Report (YSR) [38] - a widely used questionnaire, derived from the Child Behavior Check List (CBCL), for use by 11-18-year-olds. The YSR includes 112 items covering behavioral and emotional problems, which are scored on a three-point scale ('certainly applies', 'somewhat applies' and 'does not apply', scored 2, 1 and 0, respectively). The YSR total problem score taps withdrawal, somatic complaints, anxiety/depression, thought problems, social problems, attention problems, delinquent behavior and aggressive behavior.

### Confounders

We considered potential confounders related to sGC treatment and child mental health which were available in the cohort. Socio-demographic factors previously associated with ADHD symptoms were: sex, maternal age (years), maternal education (either  $\geq 11$  years of education or  $< 11$  years of education, coded 0 or 1, respectively) and family structure (either married/co-habiting or single/widowed/divorced, coded 0 or 1, respectively) [39-41]; the latter three factors were measured at recruitment. Medical factors previously associated with child mental health or relevant for this study were: gestational age [42], total prenatal sGC dose (mg), interval between prenatal sGC exposure and birth (days), parity (continuous) [43], pre-pregnancy body mass index (BMI) (pre-pregnancy weight [kg] / height<sup>2</sup> [m<sup>2</sup>]) (continuous) [32], and smoking during pregnancy (no/yes, coded 0/1, respectively) [40]. We obtained data on the main pregnancy complications related to pre-term birth from hospital records: gestational hypertension (no/yes), pre-eclampsia (no/yes) and placenta previa (no/yes).

### Statistical Analysis

We used two analytical strategies to analyse the data: (1) analysis of the propensity-score-matched subsample by linear multiple regression, and (2) analysis of the entire sample by mixed-effects modeling. All main analyses were performed using SPSS 20.0, while the power analysis was run using G\*Power 3 [44].

### Descriptive Analysis

We carried out descriptive analyses of all covariates potentially associated with sGC treatment, by means of t-test or chi-square statistics. Further, we examined whether there were any significant differences between matched cases and controls (within the propensity-score-matched subsample) by the covariates by means of t-test or chi-square statistics.

We performed attrition analyses at each follow-up to determine any differences in socio-demographics, birth outcomes and mental health outcomes between participants and non-participants.

### Matching Procedure

We used two matching procedures. First, we used propensity-score-matching [45] to match sGC cases and controls. The propensity score is the probability of treatment assignment based on observed baseline covariates. Matching on the propensity score creates balance, i.e. similarity, between cases and controls on the distribution of baseline covariates and thus reduces confounding associated with receipt of treatment. This matching technique mimics the randomization procedure prior to treatment allocation in a Randomized Controlled Trial (RCT). Thus, propensity-score-matching facilitates estimation of treatment effects using observational data.

The covariates associated with sGC treatment were included as predictors in the logistic regression model used to calculate the propensity scores. The propensity scores were log transformed to normalize the distribution of the scores. sGC cases were matched to controls on the logit propensity score, using "nearest neighbour matching" with a caliper width (matching range) of  $\pm 0.171402$  (0.2 SD of the mean logit of the propensity score) [46]. We capitalized on our large dataset by matching each sGC case to 5 controls; ratio matching has been shown to be advantageous, and the optimum matching is normally reached with 5 matches to a single case [47]. This resulted in a sample of 222 children at 8 years (sGC cases, n=37; controls, n=185) and a sample of 174 adolescents at 16 years (sGC cases, n=29; controls, n=145).

The second matching procedure took full advantage of the entire cohort by matching each sGC case, n=37, to all possible controls, n=6079, on gestational age and sex – confounders selected based on *a priori* information. Pre-term birth is a well-known risk factor for poor mental health outcomes [42] and is associated with gestational complications [48]. There is evidence that male fetuses are more vulnerable to prenatal insults [49], and are at an increased risk of psychiatric disturbance in childhood [41,50]. Thus, by matching on these known risks, we were able to isolate the impact of prenatal

sGC exposure on mental health from the confounding effects of pre-term birth and sex.

A "grouping" variable, based on gestational age and sex, was used to match the cases and controls. There were no sGC cases born within gestational weeks 41 to 43, therefore the 2229 controls born within those gestational ages could not be compared with the cases and consequently excluded from all subsequent analyses. At 8 years, 6116 children were available for analysis (sGC cases, n=37; controls, n=6079) and by 16 years of age, 5108 adolescents participated (sGC cases, n=29; controls, n=5079). This analytical strategy allowed us to use the greatest number of possible controls per case, thereby enhancing the precision of the analysis by maximizing use of all the available data [51].

### Regression Models

We used linear multiple regression to investigate the association between prenatal sGC treatment and child mental health, within the propensity-score-matched subsample. Prenatal sGC treatment was dichotomized: sGC case (coded 1) and sGC control (coded 0). The mental health scores were continuous. We adjusted for all potential confounders as shown by our descriptive analysis or by previous research. We used Cohen's  $f^2$  as an effect size estimator for the associations.

We used mixed-effects modeling to re-analyse the association between prenatal sGC and mental health, but here we used the entire cohort. In this way, we can determine if the results are replicable or merely due to certain characteristics in the subsample. This statistical technique is robust in the analysis of unbalanced data, and thus is suitable here where there are unequal numbers of cases and controls. In the model, the predictor (prenatal sGC) and confounders were included as fixed effects. The "grouping" variable, based on gestational age and sex, was included as a random effect, thus allowing the model representing the impact of sGC on mental health to vary as a function of the group, thereby reducing the confounding effects of pre-term birth and sex.

### Mediation Analysis

We used the bootstrap method [52,53] to evaluate whether birthweight and placental weight mediated the possible association between prenatal sGC and mental health, within the propensity-score-matched subsample. This is a resampling method which generates accurate confidence intervals to assess mediation effects. Bootstrapping does not impose any assumption about the shape of the distribution of the mediation effect, and thus it has been suggested that it is a more powerful technique than single sample methods [52,54].

### Power Analysis

We performed a *post hoc* power analysis to determine whether our study was sufficiently powered to detect any possible significant impact of sGC treatment, at 8 years and 16 years.

## Results

### Descriptive Analysis

Table S1 shows pregnancy and birth characteristics for the unmatched cases and controls, available for analysis. Prior to propensity-score-matching, sGC cases and controls differed significantly on gestational age, birthweight, and placental weight. The difference on pre-pregnancy BMI was significant,  $p=.04$  (based on all treated cases,  $n=41$ ). As gestational age and pre-pregnancy BMI precede sGC treatment, these covariates were included in the propensity-score model.

Table 1 shows pregnancy and birth characteristics for the propensity-score-matched cases and controls. There were no significant differences between the matched sGC cases and controls on any of the socio-demographic or medical factors. Importantly, there were no significant differences on gestational age and pre-pregnancy BMI, nor on the mean logit propensity score (case mean=-4.35; control mean=-4.36;  $p=.96$ ) – indicating balance between cases and controls on treatment-associated confounders.

Table S2 shows the attrition analyses among sGC cases from birth to 8 years, and from 8 years to 16 years. There were no significant differences by socio-demographics and birth outcomes between the participants and non-participants at 8 years. Similarly, attrition was not characterised by any significant differences from childhood to adolescence by socio-demographics, birth outcomes and mental health (at 8 years).

While all the sGC cases were hospitalized, only one sGC case experienced one of the main pregnancy complications related to pre-term birth (gestational hypertension, pre-eclampsia or placenta previa). This single case did not significantly impact upon the mean mental health scores, and therefore was included in all analyses. Out of the controls, approximately 15% were hospitalized and 9% experienced the main pregnancy complications related to pre-term birth.

### Regression Models

Table 2 shows the linear multiple regression results for the association between prenatal sGC treatment and mental health outcomes in children and adolescents, controlled for sex, birthweight, placental weight, socio-demographic factors (maternal age, education and family structure), and medical factors (total prenatal sGC dose, interval between prenatal sGC exposure and birth (days), parity and smoking during pregnancy). There were significant associations between prenatal sGC treatment and the total Rutter and inattention scores, at 8 years. The effect sizes for the total Rutter, inattention-hyperactivity, inattention and antisocial scores were moderate, while the association for the hyperactivity score showed a large effect size. Similar to the results at 8 years, we found consistent significant associations between prenatal sGC treatment and each of the outcome scores at 16 years; however, these did not reach statistical significance.

Table 3 shows that the mixed-effects model produced very similar results to the first analysis. Prenatal sGC treatment was significantly associated with the total Rutter and inattention scores at 8 years, and was consistently associated with higher scores on all other outcomes at 8 and 16 years. Additionally,

this method revealed neurotic scores were also elevated among sGC cases in comparison to controls at 8 years.

### Mediation Analysis

The bootstrap method showed that there were no significant indirect effects of birthweight (e.g. for total Rutter score, bootstrap estimate=.67, percentile 95% CI=-1.33-3.00) or placental weight (e.g. for total Rutter score, bootstrap estimate=.24, percentile 95% CI=-1.07-2.00) on the sGC-mental health pathway. Thus, we did not find evidence for mediation by birthweight or placental weight.

### Power Analysis

The *post hoc* power analysis showed that the study had sufficient power to detect significant differences at 8 years (e.g. for total Rutter score model,  $1-\beta=.80$ , with an effect size  $f=.23$  and  $p=.05$ ), but was under-powered at 16 years (e.g. for combined ADHD score model,  $1-\beta=.39$ , with an effect size  $f=.11$  and  $p=.05$ ).

## Discussion

This study is the first to explore the long-term associations between prenatal exposure to sGC treatment and mental health in childhood and adolescence. We found that both children and adolescents prenatally exposed to sGC scored consistently higher on internationally validated screening instruments of mental health, by teacher, parental and self-reports, than controls. The propensity-score-matched subsample showed that prenatal exposure to sGC treatment was significantly associated with the total Rutter and inattention scores in childhood, independent of relevant confounders – sex, birthweight, placental weight, socio-demographic factors and medical factors. Past studies have in particular found it challenging to disentangle the effect of prenatal sGC on mental health from pre-term birth, which is associated with both sGC treatment and child mental health. Through propensity-score-matching, cases and controls were balanced, i.e. matched, on gestational age and pre-pregnancy BMI, and so we were able to isolate the impact of prenatal sGC on mental health from these treatment-associated confounders. Therefore, our findings suggest that prenatal sGC is a potential programming agent of child mental health, rather than a mere epiphenomenon. We examined the robustness of our findings by testing the association using the entire cohort by means of mixed-effects modeling. We found very similar results using the entire sample compared with the subsample, providing further evidence that our results are unlikely to be affected by confounding.

We set out to examine the potential long-term association between prenatal sGC exposure and mental health, and therefore studied adolescents by way of parental-report specific for ADHD symptoms and self-report for general mental health. Given attrition by the 16-year follow-up, only 29 cases remained for analysis which left our study under-powered at this point – as confirmed by our power analysis. Nonetheless, the pattern of associations at 16 years was consistent with the findings reported at 8 years.

**Table 1.** Pregnancy and birth characteristics for the sGC cases\* (n=37) and matched controls (n=185); 1:5 matching ratio, matched on logit of propensity score.

Characteristic	Mean ± SD or n (%)		P
	Case	Control	
<b>Pregnancy</b>			
Maternal age (years)	29.2 ± 5.0	27.6 ± 5.2	.10
Family structure			.37
Married/co-habiting	36 (97.3)	173 (93.5)	
Single/widowed/divorced	1 (2.7)	12 (6.5)	
Education (years)			.92
<11	10 (31.3)	54 (32.1)	
≥11	22 (68.8)	114 (67.9)	
Parity			.98
0	11 (29.7)	60 (32.4)	
1	16 (43.2)	76 (41.1)	
2	5 (16.2)	32 (17.3)	
≥ 3	4 (10.8)	17 (9.2)	
Smoking during pregnancy			.17
No	31 (86.1)	137 (75.7)	
Yes	5 (13.9)	44 (24.3)	
Pre-pregnancy BMI	21.1 ± 2.5	20.5 ± 2.6	.22
Pre-pregnancy BMI categories			.44
< 20	14 (37.8)	87 (47.0)	
20-24.99	20 (54.1)	90 (48.6)	
≥ 25	3 (8.1)	8 (4.3)	
<b>Main pregnancy complications – risk for pre-term birth</b>			
Gestational hypertension	0 (.0)	13 (7.1)	.23
Preeclampsia	4 (5.3)	4 (2.2)	.41
Placenta previa	0 (.0)	1 (.5)	.65
Total sGC dose (mg)	15.4 ± 4.8		
<b>Interval between prenatal sGC exposure and birth (days)</b>			
6-14	5 (13.5)		
15-23	0 (.0)		
24-32	5 (16.2)		
33-41	8 (21.6)		
41-49	10 (27.0)		
50-58	4 (10.8)		
59-67	2 (5.4)		
≥ 68	2 (5.4)		
<b>Birth</b>			
Sex			.86
Male	18 (51.4)	98 (53.0)	
Female	18 (48.6)	87 (47.0)	
Gestational age at birth (weeks)	37.2 ± 2.0	37.5 ± 2.0	.60
Gestational age categories (weeks)			.90
Pre-term birth (< 37)	10 (27.0)	48 (25.9)	
Term birth (≥ 37)	27 (73.0)	137 (74.1)	
Birthweight (g)	3159 ± 688	3151 ± 636	.65
Birthweight categories (g)			.59
< 2500	6 (16.2)	23 (12.4)	
2500-4499	30 (81.1)	160 (86.5)	
≥ 4500	1 (2.7)	2 (1.1)	
Placental weight (g)	586 ± 139	588 ± 135	.96
Placental weight categories (g)			.80
< 550	14 (37.8)	75 (40.8)	
550-719	17 (45.9)	84 (46.7)	

**Table 1 (continued).**

Characteristic	Mean ± SD or n (%)		P
	Case	Control	
≥ 720	6 (16.2)	25 (13.6)	

a. Including cases exposed to prenatal sGC > 4 days prior to birth.

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**Table 2.** Linear multiple regression results for the association between prenatal glucocorticoid treatment (cases<sup>a</sup>, n=37 (at 8y) n=29 (at 16y), and controls balanced on gestational age and pre-pregnancy BMI, by means of logit of propensity score, 1:5 matching ratio) and mental health outcome scores for children and adolescents, adjusted for relevant confounders<sup>b</sup>.

Mental Health	Prenatal glucocorticoid (GC) treatment (case/control)									
	Unadjusted					Adjusted <sup>c</sup>				
	B	95% CI for B	β	P	B	95% CI for B	β	P	Cohen's f <sup>2</sup>	
<b>8-y-olds (Rutter (teacher report))</b>										
Total Rutter score	1.07	-.95-3.10	.08	.30	8.34	-.23-16.45	.56	.04	.23	
Antisocial score	.28	-.45-1.00	.05	.45	2.93	-.04-5.9	.54	.05	.20	
Neurotic score	.11	-.39-.62	.03	.66	1.55	-.55-3.67	.42	.15	.11	
Inattention-hyperactivity score	.21	-.40-.72	.04	.56	2.16	-.03-4.35	.52	.05	.33	
Inattention score <sup>d</sup>	-.02	-.23-.18	-.02	.81	.97	.16-1.80	.64	.02	.23	
Hyperactivity score <sup>e</sup>	.19	-.21-.58	.07	.35	1.19	-.29-2.67	.41	.12	.36	
<b>16-y-olds SWAN (parent report)</b>										
Combined ADHD score	-1.15	-3.48-6.19	-.03	.76	16.20	-14.65-47.04	.34	.30	.11	
Inattention score <sup>f</sup>	-.53	-4.31-3.24	-.02	.78	9.00	-6.42-24.41	.37	.25	.11	
Hyperactivity score <sup>f</sup>	-.61	-4.60-3.38	-.02	.76	7.20	-9.85-24.26	.27	.41	.10	
<b>18-y-olds YSR (self-report)</b>										
YSR Total Problem score	2.10	-4.55-6.74	.05	.53	2.30	-28.43-31.00	.05	.88	.12	

a. Including cases exposed to prenatal sGC > 4 days prior to birth.

b. adjusted for sex, birthweight, placental weight, socio-demographic factors (maternal age, education and family structure), and medical factors (total prenatal sGC dose, interval between prenatal sGC exposure and birth (days), smoking during pregnancy and parity).

c. score based on Rutter item number 16 (range 0 to 2).

d. score based on sum of Rutter items 1 and 3 (range 0 to 4).

e. score based on sum of 9 SWAN items (range -27 to 27).

f. score based on sum of 9 SWAN items (range -27 to 27).

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Our findings corroborate and extend previous results of observational studies of high-risk pregnancies in humans, which have examined the effect of repeat prenatal sGC doses on child mental health [15,16]. Most previous studies have used high-risk samples in comparison to normal pregnancies, making it difficult to differentiate between medical complications that prompted treatment and the potential effect of the treatment itself on the outcome. Ours is a community cohort in which both controls and cases experienced pregnancy complications and were hospitalized. Out of the controls, approximately 9% experienced the most common causes of pre-term birth (gestational hypertension, pre-eclampsia and placenta previa) and 15% were hospitalized. Only one case experienced one of the most common causes of pre-term birth. In this sense, our results are more generalizable, rather than specific to high-risk sub-groups and so are unlikely to be affected by confounding of pregnancy complications.

We were able to examine the impact of fairly low and infrequent doses of prenatal sGC (the average total dose was 15.4mg and the maximum dosage was approximately equal to a single course of sGC, according to current guidelines). Given the concerns raised by use of repeat sGC in pregnancy [14,22] and the call for longitudinal research [55], it is of public health interest to study long-term risks associated with exposure at this low dosage. Our findings suggest that even at low dosages the fetal brain may be sensitive to sGC. Interestingly, we found that prenatal sGC had a non-specific effect on child mental health, as indicated by an association with the total Rutter, which reflects a range of emotional and behavioral problems, including ADHD symptoms. A total Rutter score of ≥9 indicates probable psychiatric disturbance, and so the mean Rutter score difference of approximately 8 points between cases and controls reflects clinical significance.

Cortisol may directly impact brain development because glucocorticoid receptors (GR) and mineralocorticoid receptors

**Table 3.** Mixed-effects model for the association between prenatal glucocorticoid treatment (case' vs. control, matched for gestational age and sex) and mental health outcome scores for children and adolescents, adjusted for relevant confounders<sup>a</sup>.

Mental health	Prenatal glucocorticoid (GC) treatment (case/control)							
	Estimates				Pair-wise comparisons			
	n	Means	SE	95% CI	Mean difference (B)	SE	95% CI	P
<b>8-y-olds Rutter (teacher report)</b>								
Total Rutter score					8.04	3.34	1.49-14.60	.02
GC control	6059	3.59	.32	2.90-4.28				
GC case	37	11.63	3.33	5.11-18.15				
Antisocial score					2.15	1.12	-0.04-4.35	.05
GC control	6065	.75	.11	.50-1.00				
GC case	37	2.90	1.11	.72-5.01				
Neurotic score					2.48	.84	.84-4.12	.00
GC control	6076	.65	.02	.61-.70				
GC case	37	3.13	.83	1.50-4.76				
Inattention-hyperactivity score					1.53	1.01	-.43-3.51	.13
GC control	6069	3.86	.11	3.62-4.09				
GC case	37	5.39	1.00	3.43-7.36				
Inattention score <sup>c</sup>					.79	.35	-.12-1.47	.02
GC control	6079	.22	.03	.16-.29				
GC case	37	1.01	.34	.34-1.69				
Hyperactivity score <sup>d</sup>					.74	.73	-.69-2.17	.31
GC control	6075	2.63	.08	2.45-2.81				
GC case	37	3.37	.73	1.95-4.80				
<b>16-y-olds SWAN (parent report)</b>								
Combined ADHD score					13.82	12.83	-11.22-39.08	.28
GC control	4950	-20.23	.86	-22.10--18.36				
GC case	29	-6.31	12.77	-31.34-18.72				
Inattention score <sup>e</sup>					8.42	6.80	-4.91-21.74	.22
GC control	4950	-8.00	.49	-9.05--6.94				
GC case	29	.42	6.77	-12.85-13.69				
Hyperactivity score <sup>f</sup>					6.47	6.99	-9.24-19.17	.43
GC control	4950	-12.22	.38	-13.05--11.38				
GC case	29	-6.75	6.96	-20.39-6.89				
<b>16-y-olds YSR (self-report)</b>								
YSR Total Problem score					16.39	12.05	-7.24-40.02	.17
GC control	5079	25.52	1.34	22.67-28.36				
GC case	29	41.91	12.03	18.33-65.49				

a. Including cases exposed to prenatal sGC > 4 days prior to birth.

b. adjusted for birthweight, placental weight, socio-demographic factors (maternal age, education and family structure), and medical factors (total prenatal sGC dose, interval between prenatal sGC exposure and birth (days), smoking during pregnancy, parity and pre-pregnancy BMI).

c. score based on Rutter item number 16 (range 0 to 2).

d. score based on sum of Rutter items 1 and 3 (range 0 to 4).

e. score based on sum of 9 SWAN items (range -27 to 27).

f. score based on sum of 9 SWAN items (range -27 to 27).

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(MR), both of which have a high affinity for GC, are highly expressed in the fetal brain [56], particularly the hippocampus [57]. Animal studies have shown that prenatal sGC exert widespread effects on the developing brain, reducing neuron proliferation [58], as well as affecting neuron structure and synapse formation [59]. Prenatal sGC has been linked with reduced density of hippocampal neurons in the offspring, in both humans and animals [57,60]. Altered hippocampal

structure in turn has been associated with mental health, including ADHD [61,62]. A recent study demonstrated that prenatal sGC was associated with thinner brain cortex in children, which in turn was linked with affective problems [63]. There is also evidence that prenatal sGC has a long-term impact on hypothalamic-pituitary-adrenal (HPA) axis reactivity in term-born children, which may bear significant implications for stress-related psychiatric disorders [64].

We tested the hypothesis that deviation in birthweight or placental weight would mediate the association between prenatal exposure to sGC and child mental health. It is possible that altered birth size and/or placental size, both of which have been linked to prenatal sGC exposure [22,27] and child mental health [23,29], would lie on the GC programming pathway. However, we did not find support for this idea.

As in all longitudinal studies, attrition occurs at every follow-up and is the main limitation. With a loss of 9 cases by the 16-year follow-up, our study was under-powered at this point, which is a likely explanation for non-significant findings at this age. The NFBC 1986 is a prospective cohort but was not designed to examine sGC treatment outcomes - we performed a chart review to identify sGC cases, thus we cannot rule out the impact of unmeasured confounders. It is not possible to completely rule out that the observed differences in mental health scores may be due to the complications of pregnancy which prompted sGC treatment. However, this seems unlikely here as both cases and controls experienced pregnancy complications, and our matching procedures ensured that cases and controls were balanced on important confounders. Due to the very small number of sGC cases experiencing pregnancy complications known to be a risk for pre-term birth ( $n=1$ ), we could not study these as sub-groups. Further work is required to determine the impact of pregnancy complications on later mental health with larger samples. Finally, sGC cannot be directly equated to endogenous maternal GC. sGC and endogenous GC largely bind to different types of steroid receptors and so may have different biological effects. Despite these limitations, sGC provides a useful quasi-experimental model in the absence of direct experimental manipulation in humans and provides a tentative proof of concept, warranting further research to better understand the associations and their underlying mechanisms.

Our study has important strengths. First, we used propensity-score-matching to account for treatment-selection bias (thereby partly mimicking an RCT), in particular gestational age and pre-pregnancy BMI, and so we were able to isolate the effect of the drug from these two significant confounders associated with receipt of treatment. Our large dataset enabled us to very precisely match cases to controls on the logit propensity scores. Thus the results presented here are not due to prematurity, which its threat would prompt treatment, and is known to be a risk for poor neurodevelopmental outcomes, including ADHD [65,66] nor pre-pregnancy BMI which was also associated with treatment in this sample as well as ADHD [32,67]. The matched cases and controls were also balanced on other important confounders, and these confounders were additionally adjusted for in the main analysis. Thus, we minimized confounding related to sGC treatment and mental health as much as possible. Second, we were able to replicate the results produced from the propensity-score-matched subsample using the entire cohort by means of mixed-effects modeling, demonstrating the robustness of our findings. Third, we used precise case classification (exposed >4 days prior to delivery) to ensure that the drug had sufficient time to act on

the fetal brain. Studies which do not take exposure time into consideration e.g. Dalziel et al. (2005) may be more likely to report null findings as the drug may not have had time to act on the fetal brain. Fourth, we assessed child and adolescent mental health via multiple informants and multiple validated instruments, which strengthen the credibility of the results and extend previous findings that have relied almost completely on parental report. Fifth, we address the growing public health concern regarding side-effects of sGC treatment by studying the impact of fairly low/infrequent doses of sGC.

In conclusion, the data we present here, originating from a population-based cohort, is the largest to date and show an association between prenatal sGC exposure and child mental health. Further work is necessary to confirm the long-term associations. By capitalizing on the natural experiment in which women are treated with sGC, we were able to explore the hypothesized pathway between fetal glucocorticoid exposure and later child mental health. The results show that this pathway merits further scientific research, though it is a challenge using human studies. While the benefits of prenatal sGC treatment on the immediate health and survival of the pre-term neonate are clear, it is also important to consider the long-term health implications of this drug, including those relating to mental health. The clinical ramifications of this study call for close monitoring of children prenatally exposed to sGC in order to provide support early if mental health problems arise.

## Supporting Information

**Figure S1. Flowchart of systematic screening process to identify sGC cases within the NFBC 1986.**  
(TIF)

**Table S1. Pregnancy and birth characteristics for the sGC cases\* ( $n=37$ ) and controls ( $n=8018$ ), available for analysis.**  
(DOCX)

**Table S2. Attrition analyses from birth to 8 years and 8 to 16 years, among sGC cases\*.**  
(DOCX)

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## Author Contributions

Conceived and designed the experiments: AR NK VG MJ. Analyzed the data: NK. Contributed reagents/materials/analysis tools: MJ AT HE. Wrote the manuscript: NK AR. Responsible for cohort data integrity: AT. Contributed to the manuscript, read and approved the final version: NK VG AT HE MJ AR.

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**From:** Boghossian, Nansi (NIH/NICHD) [F]  
**To:** Higgins, Rosemary (NIH/NICHD) [F]  
**Subject:** FW: Pediatrics - 2013-1702.R2  
**Date:** Tuesday, November 26, 2013 10:09:22 AM

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Our paper will appear in the Feb Pediatrics issue.

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

**From:** Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]  
**Sent:** Tuesday, November 26, 2013 10:06 AM  
**To:** Boghossian, Nansi (NIH/NICHD) [F]; Nellie Hansen  
**Subject:** FW: Pediatrics - 2013-1702.R2

We made the print issue!

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

**From:** onbehalfof+martha.andreas+uvm.edu@manuscriptcentral.com  
[mailto:onbehalfof+martha.andreas+uvm.edu@manuscriptcentral.com] On Behalf Of martha.andreas@uvm.edu  
**Sent:** Tuesday, November 26, 2013 9:00 AM  
**To:** Bell, Edward (Pediatrics)  
**Subject:** Pediatrics - 2013-1702.R2

26-Nov-2013

RE: 2013-1702.R2 - Mortality and Morbidity of VLBW Infants with Trisomy 13 or Trisomy 18

Dear Dr. Bell:

We would like inform you that your article has been selected for the February 2014 Print and online issues of Pediatrics. If you have already seen received page proofs from our publisher, you should be aware of the following:

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**From:** Tyson, Jon E  
**To:** Wally Carlo (wacar10@uab.edu) (wacar10@uab.edu); Walsh, Michele (Michele.Walsh@UH-hospitals.org); Finer, Neil; Abhik Das (Adas@rti.org) (Adas@rti.org)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A  
**Subject:** FW: OHRP presentation regarding the SUPPORT trial  
**Date:** Monday, November 25, 2013 6:37:05 PM  
**Attachments:** Charles Natanson.pptx

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In revising the Misconceptions about SUPPORT paper to submit for publication, I have been reviewing the presentations from the ORHP meeting. I think you will want to review the comments made in this presentation by the Chief of Anesthesia Section (Critical Care Medicine Dept) at the NIH and a Professor at U Maryland and Johns Hopkins. I sent my questions and comment to him, being careful to indicate I don't represent the Network (though I hope none of you feel I missed something important). While I disagree with his conclusion, criticism coming from someone of his caliber who works at NIH is worth careful consideration. This kind of criticism he makes is one that we will want to be ready to defend ourselves against if need be in future publications about SUPPORT or in court. On a quick read of the now available Saugstad meta-analysis, I couldn't tell from whether a treatment x algorithm interaction was tested. However, Natanson contends that the effects of the oxygen saturation group differs with the two algorithms, indicating that questions of the kind I raised in my last e mail may well be asked by others.

I hope you all have a great Thanksgiving. I hope my e mails won't cause indigestion.

. ----Original Message-----

**From:** Tyson, Jon E  
**Sent:** Monday, November 25, 2013 1:45 PM  
**To:** 'cnatanson@cc.nih.gov'  
**Subject:** Your OHRP presentation regarding the SUPPORT trial

I am a clinical investigator, and a participant in the NICHD Neonatal Network since its inception. I was involved an investigator (though not a PI) in SUPPORT, spoke at the OHRP meeting, and have been reviewing all of the presentations. Your slides are particularly interesting in trying to more clearly understand the confusing results of the different saturation trials. Thanks for conducting and reporting your analyses so clearly. They may help advance the discussion about these trials. I would appreciate your thoughts about a few questions and comments (which of course don't necessarily represent the views or attitudes of any of my colleagues in the Network):

1. You indicated that the OR of survival with the original algorithm calibration in the meta-analysis of the UK, Australia, and Canada trial was not significant. Did you determine the OR and p value if the Network trial was added? If still not significant (as I would assume), would you (and your statistician) conclude that is unclear whether or not the significantly higher mortality with the lower saturation goal in using the lower algorithm in the Network trials was due to the play of chance?
2. How were the p values calculated in assessing the changes before and after the change in algorithm in the UK, Australia, and Canada trials? How was the  $p=0.01$  on the next to last slides calculated? Was there a significant treatment x algorithm interaction? Do you consider the results of the analyses to be hypothesis confirming or hypothesis generating (as I believe the editors of the New Engl J Medicine would contend by their requirements for sublyses)?
3. You indicate that the narrower, more bell shaped distribution of oxygen saturation curves with the revised algorithm resulted in a different effect on mortality in the two groups with lower mortality in the high saturation group and a tred toward a higher mortality in the low saturation groups--relative to that with the wider bimodal saturation distribution with the original algorithm. However, it is unclear why you use the term "usual care" in the inferences in your sentences restated below.

A. "Decreasing oxygen exposure improved survival rates in preterm babies already receiving levels higher than usual care."

As I understand your slides, you report that the high saturation group (91%-95% saturation goal) generally spent less time with true saturations of 91% or greater with the revised algorithm than they did with the original algorithm and more time with saturations of 85-90%. You don't present data for time spent with saturations below 85-89%, particularly below say 70%, which may be when low saturation are most likely to increasing mortality. However, assuming that there is no important difference between the high saturation goal group in time spent below with such low saturations before and after changing the algorithm, there are no data indicating that when the original algorithm was used, the high saturation goal group spent a higher proportion of time with high oxygen saturations than occurs in usual clinical care in study centers or in typical neonatal ICUs.

Indeed, the opposite may be true. The trial involved considerable effort to avoid extreme saturation values outside the target range. This included great effort to assure that the NICU staff who routinely dial up the FiO<sub>2</sub> when infants have apneic episodes or desaturations for any other reason would promptly turn dial the FiO<sub>2</sub> back down when these episodes resolved. Neonatal ICU staff are very busy and usually responsible for multiple infants, and it has been difficult to achieve staffing ratios neonatal ICUs that allow very exacting regulation of oxygen saturation in unstable individual infants. If you have spent much time in neonatal ICUs, I think you will agree that failure to promptly reduce FiO<sub>2</sub> in this situation (and temporarily raising or routinely using saturation of alarms of 98-100 to avoid frequent alarms) has been a common problem in the usual care for these infants.

If the truth were known, it wouldn't be surprising if the sentence above would be better stated as "Decreasing exposure to high saturation levels that occur with usual care was associated with a reduced mortality in the group with a saturation goal of 91-95%." Excessive oxygen exposure can increase mortality even it is brief and occurs in term infants (as is now clear from trials using restricted or 100% oxygen in delivery room resuscitation). This could be a factor, perhaps the most important factor, contributing to the lower mortality among trial infants than among historical controls and eligible infants whose parents refused consent.

B. "Decreasing oxygen exposure worsened survival rates in neonates already receiving levels lower than usual care." The data you present indicate that the infants in the 85-89 % saturation goal groups spent less time with true saturations of 91% or greater and more time at 85-90%. As evident above, its likely they also spent less time with values of 91% or greater than babies receiving usual care in clinical practice. However, there was not a significant change in mortality with the change in calibration and with the greater attention to regulating FiO<sub>2</sub> in the trial that with usual care in clinical practice, it isn't necessarily true that they spent less time than with usual care at values less than 85 or at substantially lower levels that may increase mortality.

4. The results shown on your next to last slide (which I would have no reason to challenge) do not seem to lead to the conclusions noted on the last slide for several reasons:

A. The word "extreme" is ordinarily understood to refer to values outside a particular range or to the very highest and lowest values within that range (the lowest 10% or highest 10% if not the lowest or highest 5% or 1%). Describing the ranges 85-89 and 91-95 as extreme seems unwarranted when they occupy all but the midpoint of the range 85-95.

B. If one agrees the increased attention by NICU personnel to adjust FiO<sub>2</sub> to increase the proportion of time within the goal range is a desirable feature of a clinical trial to define the preferred saturation goal, then the care given in the trial will depart from usual clinical care that involves less attention to regulating the FiO<sub>2</sub>. (The increased attention to regulation of care is of course a reason that outcomes may be enhanced for all treatment groups in clinical trials.) In this way, there would be no group representative of usual care even if the trial had included a 3rd group with a saturation goal of 85-95.

C. Studies that are needed to advance practice don't necessarily have to include any arm that represents what is truly representative of usual care.

D. Including a 3rd arm with a saturation goal of 85-95 would be expected to produce intermediate results between the two arms; would have increased the sample size, cost and effort required for the trial by at least 50% (limiting the patients, funds, and personnel time to answer other important questions); and most importantly, substantially delayed (by two years even if there was no correction for repeated analyses) when the SUPPORT results would have been reported. This would also be true for the BOOST II and COT trials. In the meantime, neonatologists

worldwide would have continued to prescribe oxygen saturation goals without any outcome data from clinical trials assessing comparing goal saturations of 85-89% or 91-95%. Its likely that an increasing number of neonatologists would have used saturation goals of 85-89% (as was my clinical practice) or lower in trying to minimize ROP and other morbidity or mortality due to excessive oxygen administration.

I appreciate your taking the time to read this and any response to me and to the Network investigators that you would feel is appropriate.

Have a happy Thanksgiving.

Jon Tyson, MD, MPH  
Vice Dean for Clinical Research and Healthcare Quality UT Houston.

# **Therapeutic Misalignment Randomization to the Extremes of Usual Care**

**Charles Natanson, M.D.**

**For critically ill patients receiving a therapy titrated to individual need, randomization to dosage extremes has foreseeable risks**

**Such trial designs, in the absence of a usual care arm, may harm patients and have a limited ability to inform practice**

# **Trials at High Risk for Therapeutic Misalignment**

- **Life-sustaining therapies routinely adjusted for severity of disease**

# **Trials at High Risk for Therapeutic Misalignment**

- **Life-sustaining therapies routinely adjusted for severity of disease**
- **Testing two extremes of such therapy**

# **Trials at High Risk for Therapeutic Misalignment**

- **Life-sustaining therapies routinely adjusted for severity of disease**
- **Testing two extremes of such therapy**
- **Therapy is changed independent of need**

# **Trials at High Risk for Therapeutic Misalignment**

- **Life-sustaining therapies routinely adjusted for severity of disease**
- **Testing two extremes of such therapy**
- **Therapy is changed independent of need**
- **No (usual care) control**

# **SUPPORT Trial**

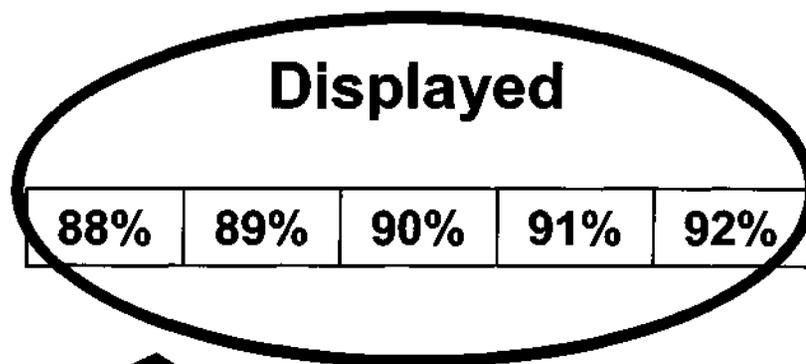
## **An Example of Therapeutic Misalignment**

# Hypothesis & Methods

- **“...a lower target range of oxygen saturation (85 to 89%), as compared with a higher ... (91 to 95%) would reduce ... severe retinopathy of prematurity or death among infants born between 24 and 27 wk ”**

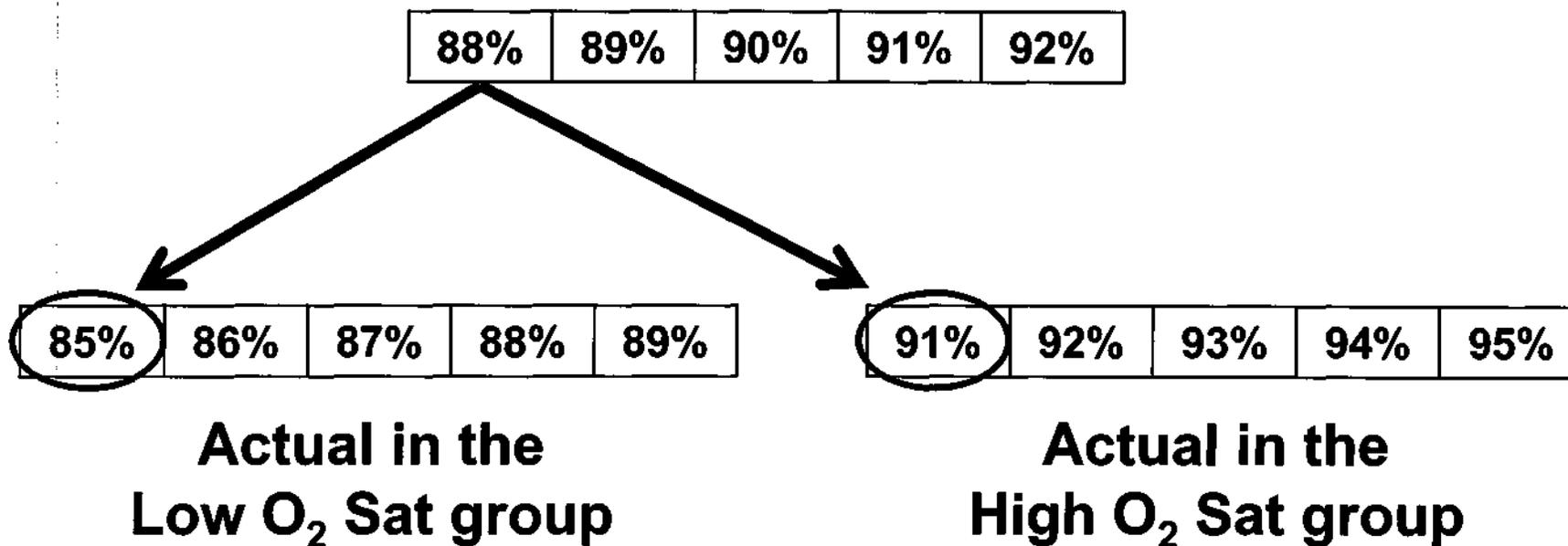
# Methods

- **In order to blind caregivers to group assignments, “offset” pulse oximeters were used to titrate oxygen therapy in preterm babies**



8 This displayed range was presumably the routine target range of O<sub>2</sub> saturations used in preterm babies %

## Displayed



**For a preterm baby with an “offset” O<sub>2</sub> Sat of 88%, the actual O<sub>2</sub> Sat could have been either 85% or 91%**

## Displayed

88%	89%	90%	91%	92%
-----	-----	-----	-----	-----

85%	86%	87%	88%	89%
-----	-----	-----	-----	-----

**Actual in the  
Low O<sub>2</sub> Sat group**

91%	92%	93%	94%	95%
-----	-----	-----	-----	-----

**Actual in the  
High O<sub>2</sub> Sat group**

**For a preterm baby with an “offset” O<sub>2</sub> Sat of 89%, the actual O<sub>2</sub> Sat could have been either 86% or 92%**

## Displayed

88%	89%	90%	91%	92%
-----	-----	-----	-----	-----

85%	86%	87%	88%	89%
-----	-----	-----	-----	-----

**Actual in the  
Low O<sub>2</sub> Sat group**

91%	92%	93%	94%	95%
-----	-----	-----	-----	-----

**Actual in the  
High O<sub>2</sub> Sat group**

**For a preterm baby with an “offset” O<sub>2</sub> Sat of 92%, the actual O<sub>2</sub> Sat could have been either 89% or 95%**

# Major Outcomes

Endpoints	O <sub>2</sub> Sat Study Groups		P-value
	Lower	Higher	
	event rate	event rate	
<b>Combined Endpoint: Severe retinopathy or death before discharge</b>	<b>28%</b> (171/605)	<b>32%</b> (198/616)	<b>0.21</b>
<b>Severe retinopathy</b>	<b>9%</b> (41/475)	<b>18%</b> (91/509)	<b>&lt; 0.0001</b>
<b>Death before discharge</b>	<b>20%</b> (130/654)	<b>16%</b> (107/662)	<b>0.04</b>

## Major Outcomes

**Because of practice misalignments created with randomization and known risks of retinopathy (higher oxygen levels) and death (lower oxygen levels) these results are not unexpected**

### **Combined Endpoint:**

**Severe retinopathy or death before discharge**

**28%**  
(171/605)

**32%**  
(198/616)

**0.21**

**Severe retinopathy**

**9%**  
(41/475)

**18%**  
(91/509)

**< 0.0001**

**Death before discharge**

**20%**  
(130/654)

**16%**  
(107/662)

**0.04**

# Major Outcomes

## O<sub>2</sub> Sat Study Groups

End **Preterm babies that were randomized to oxygen levels at the extreme HIGH end of usual care, developed more severe retinopathy** lue  
Combined Severe re 1  
death be

<b>Severe retinopathy</b>	<b>9%</b> (41/475)	<b>18%</b> (91/509)	<b>&lt; 0.0001</b>
<b>Death before discharge</b>	<b>20%</b> (130/654)	<b>16%</b> (107/662)	<b>0.04</b>

# Major Outcomes

Endpoints	O <sub>2</sub> Sat Study Groups		P-value
	Lower event rate	Higher event rate	
Com Seve deat	<div style="background-color: black; color: white; padding: 10px; text-align: center;"> <p><b>Preterm babies that were randomized to oxygen levels at the extreme LOW end of usual care died more often</b></p> </div>		<b>0.21</b>
Sev			<b>&lt; 0.0001</b>
<b>Death before discharge</b>	<b>20%</b> (130/654)	<b>16%</b> (107/662)	<b>0.04</b>

## Two Additional Trials

### Same Design and Methodology for Targeting Higher vs. Lower Oxygen Saturation Ranges with Intentionally Offset Monitors

<b>Study Name</b>	<b>Country</b>	<b>Published</b>	<b># Patients Enrolled</b>	<b>Enrollment Years</b>
<b>BOOST II</b>	<b>UK and Australia</b>	<b>NEJM 2013</b>	<b>2,448</b>	<b>2006 – 2010</b>
<b>COT</b>	<b>Canada</b>	<b>JAMA 2013</b>	<b>1,201</b>	<b>2006 – 2010</b>

# **Midway through the BOOST II and COT Trials**

- **Pulse oximeters were recalibrated**

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- **Pulse oximeters were recalibrated**
- **This resulted in an unintended experiment in the preterm babies**

# **Midway through the BOOST II and COT Trials**

- **Pulse oximeters were recalibrated**
- **This resulted in an unintended experiment in the preterm babies**
- **Potentially informative to the misalignment problem**

# Effect on Overall Survival of Recalibrating the Intentionally Offset Pulse Oximeters

## Pulse Oximeter

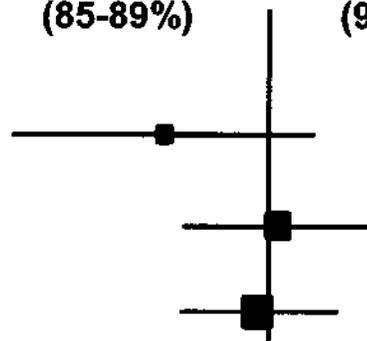
### Before Recalibration

United Kingdom

Australia

Canada

Favors Low O<sup>2</sup> Saturation Arm (85-89%)      Favors High O<sup>2</sup> Saturation Arm (91-95%)



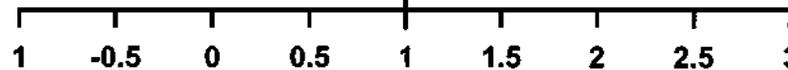
I<sup>2</sup> = 0%

### Summary Recalibration

Before



P = NS



Odds Ratio of Survival

N Engl J Med 2013;368:2094-104  
JAMA 2013;309(20):2111-20

# Effect on Overall Survival of Recalibrating the Intentionally Offset Pulse Oximeters

## Pulse Oximeter

### Before Recalibration

United Kingdom

Australia

Canada

Favors Low O<sup>2</sup> Saturation Arm (85-89%)

Favors High O<sup>2</sup> Saturation Arm (91-95%)

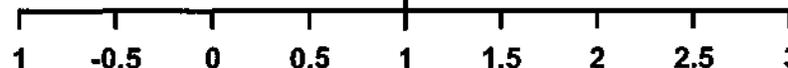
I<sup>2</sup> = 0%

Prior to recalibration, there was no significant difference in survival rates comparing the low and high oxygen target range across studies

Summary  
Recalibration

Before

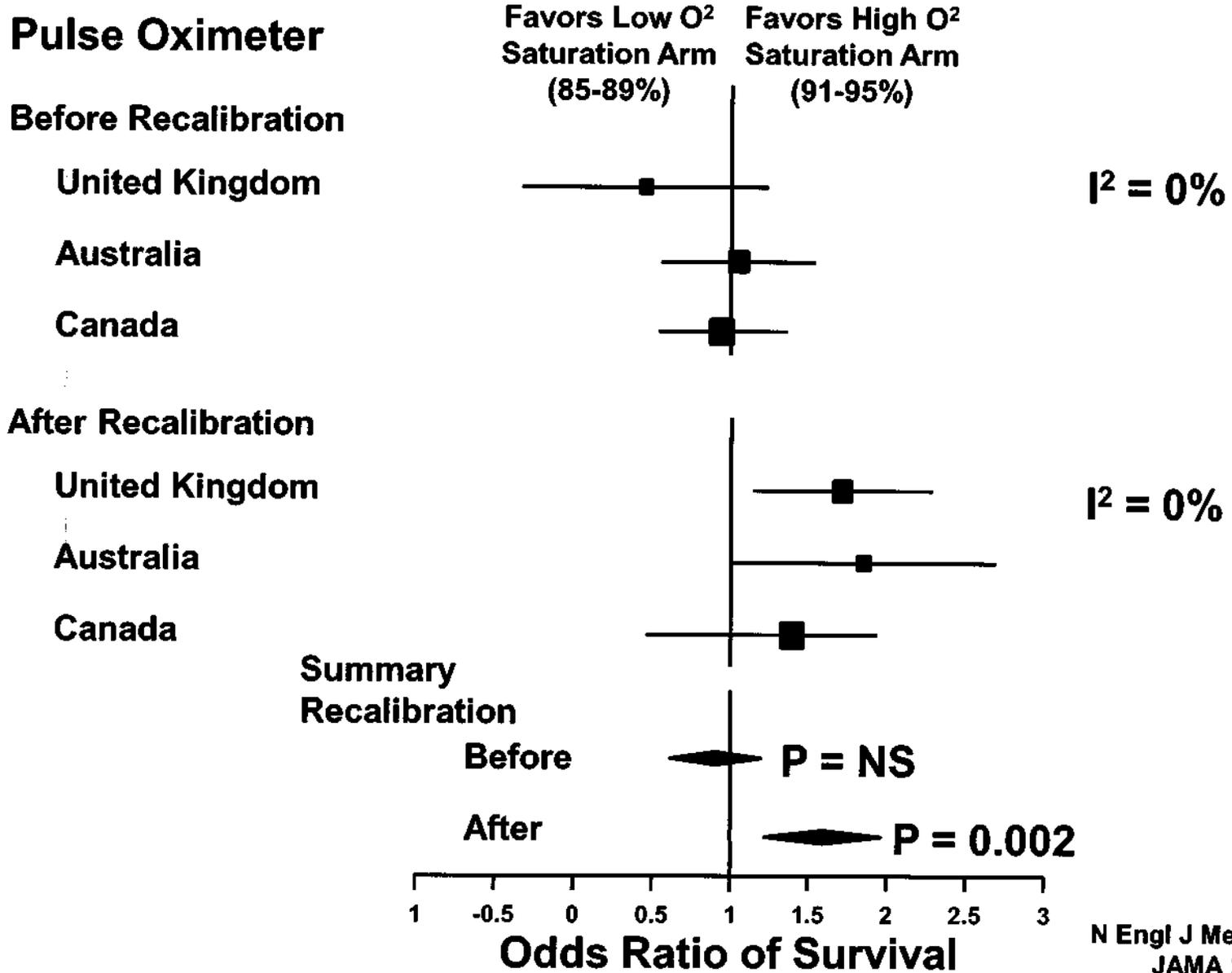
P = NS



Odds Ratio of Survival

N Engl J Med 2013;368:2094-104  
JAMA 2013;309(20):2111-20

# Effect on Overall Survival of Recalibrating the Intentionally Offset Pulse Oximeters



N Engl J Med 2013;368:2094-104  
JAMA 2013;309(20):2111-20

# Effect on Overall Survival of Recalibrating the Intentionally Offset Pulse Oximeters

## Pulse Oximeter

### Before Recalibration

United Kingdom

Australia

Canada

Favors Low O<sup>2</sup> Saturation Arm (85-89%)      Favors High O<sup>2</sup> Saturation Arm (91-95%)

I<sup>2</sup> = 0%

After recalibration, there was a significant difference in survival rates favoring the high target oxygen target range across studies

Canada

Summary Recalibration

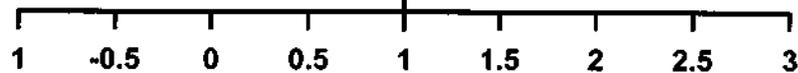
Before

After

P = NS

P = 0.002

P = 0.01



Odds Ratio of Survival

N Engl J Med 2013;368:2094-104  
JAMA 2013;309(20):2111-20

**If practice misalignments are impacting outcome, recalibrating the pulse oximeters should have the following effects:**

**If practice misalignments are impacting outcome, recalibrating the pulse oximeters should have the following effects:**

## **In the Low Oxygen**

**Lowering O<sub>2</sub> saturation should worsen, while raising O<sub>2</sub> saturation should improve outcome**

# **If practice misalignments are impacting outcome, recalibrating the pulse oximeters should have the following effects:**

## **In the Low Oxygen**

**Lowering O<sub>2</sub> saturation should worsen, while raising O<sub>2</sub> saturation should improve outcome**

**Raising O<sub>2</sub> saturation should worsen, while lowering O<sub>2</sub> saturation should improve outcome**

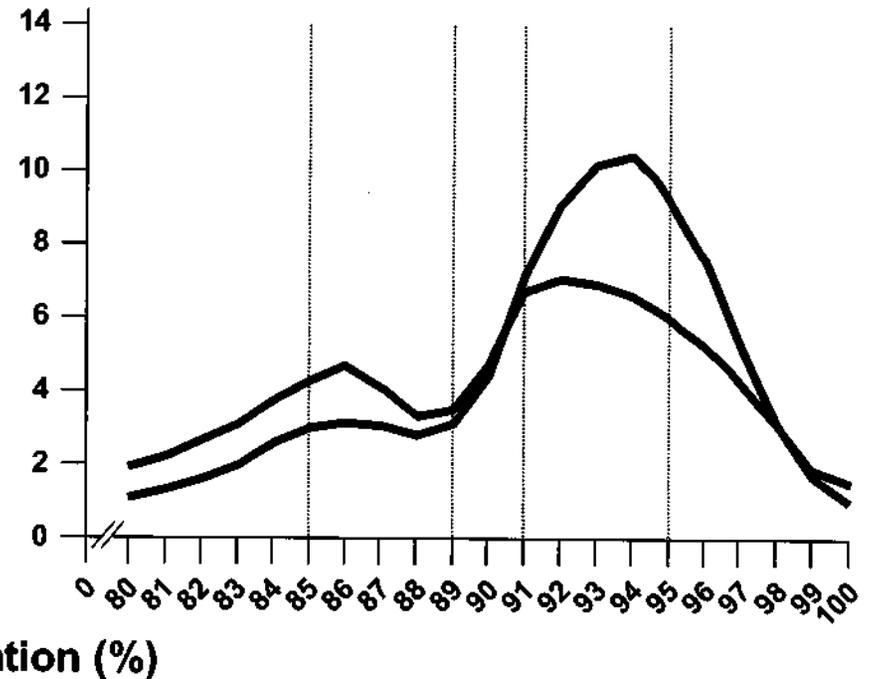
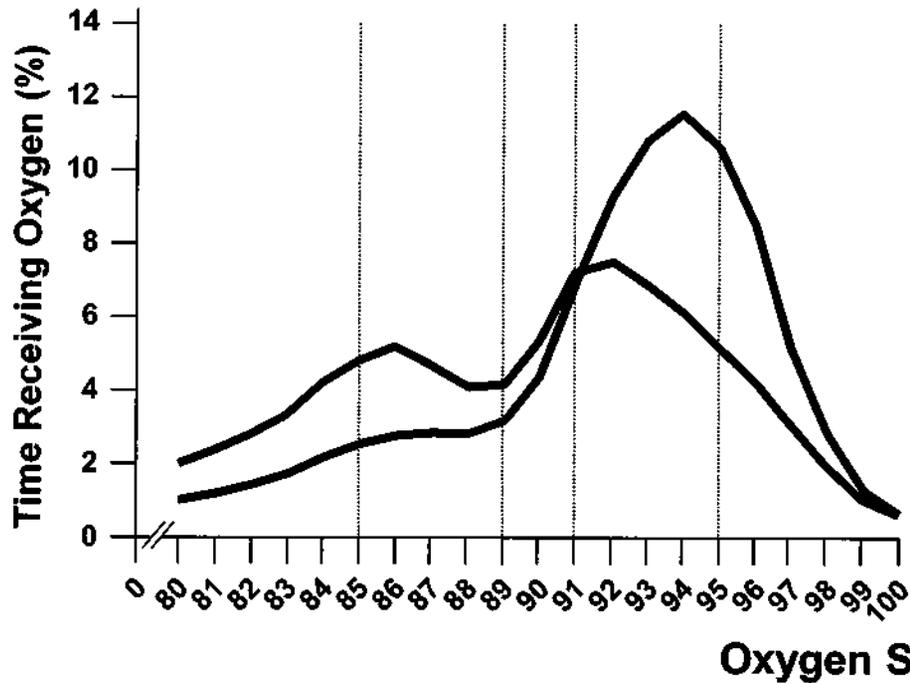
# Proportion of Time at Various O<sub>2</sub> Saturations Before Recalibration

High Target Arm (91-95%) Actual Values

Low Target Arm (85-89%) Actual Values

Australia

United Kingdom



# Changes in Oxygen Exposure from Before to After Recalibration

## Oxygen Saturation Levels Achieved

Treatment Arm and Country	Oxygen Saturation Levels Achieved	
	>95%	91-95%
<b>Proportion of time with change from before to after recalibration</b>		
<b>Low Saturation</b>		
United Kingdom	-2.2%	-2.6%
Australia	-3.0%	-3.9%
<b>High Saturation</b>		
United Kingdom	1.7%	-3.2%
Australia	-2.2%	-0.7%

# Change in Oxygen Exposure from Before to After Recalibration

## Oxygen Saturation Levels Evaluated

**Treatment Arm  
and Country**

**90%**

**85-89%**

**Proportion of time with change from before to  
after recalibration**

**Low Saturation**

**United  
Kingdom**

**2.2%** ↑

**6.3%** ↑↑

**Australia**

**2.3%** ↑

**7.9%** ↑↑

**High Saturation**

**United  
Kingdom**

**1.6%** ↑

**2.6%** ↑↑

**Australia**

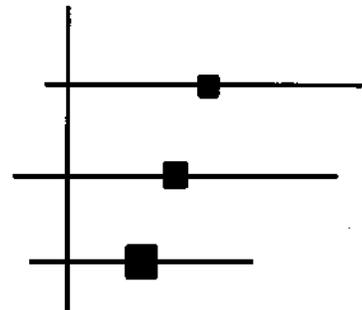
**2.1%** ↑

**3.2%** ↑↑

# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

**Treatment Arm**  
**High O<sup>2</sup> Saturation**  
**Range Arm (91-95%)**  
**United Kingdom**  
**Australia**  
**Canada**

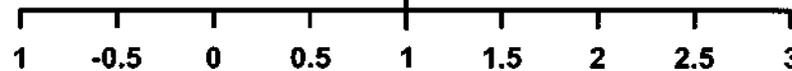
**Favors Before  
Recalibration**      **Favors After  
Recalibration**



**I<sup>2</sup> = 0%**

**Summary**

**High Arm**



**Odds Ratio of Survival**

# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

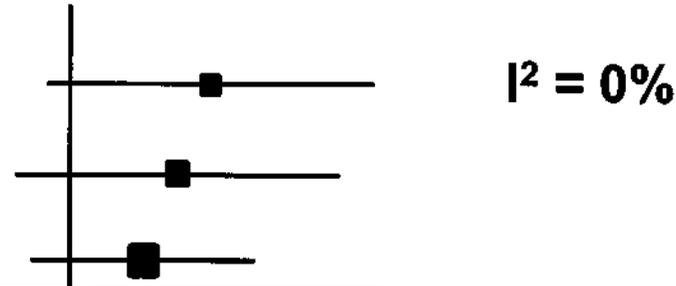
**Treatment Arm**  
High O<sup>2</sup> Saturation  
Range Arm (91-95%)

Favors Before  
Recalibration      Favors After  
Recalibration

United Kingdom

Australia

Canada

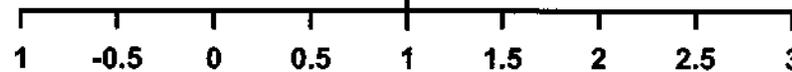


**Decreasing oxygen exposure improved survival rates in preterm babies already receiving levels higher than usual care**

Summary

High Arm

**P = 0.02**



Odds Ratio of Survival

# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

## Treatment Arm

High O<sup>2</sup> Saturation  
Range Arm (91-95%)

United Kingdom

Australia

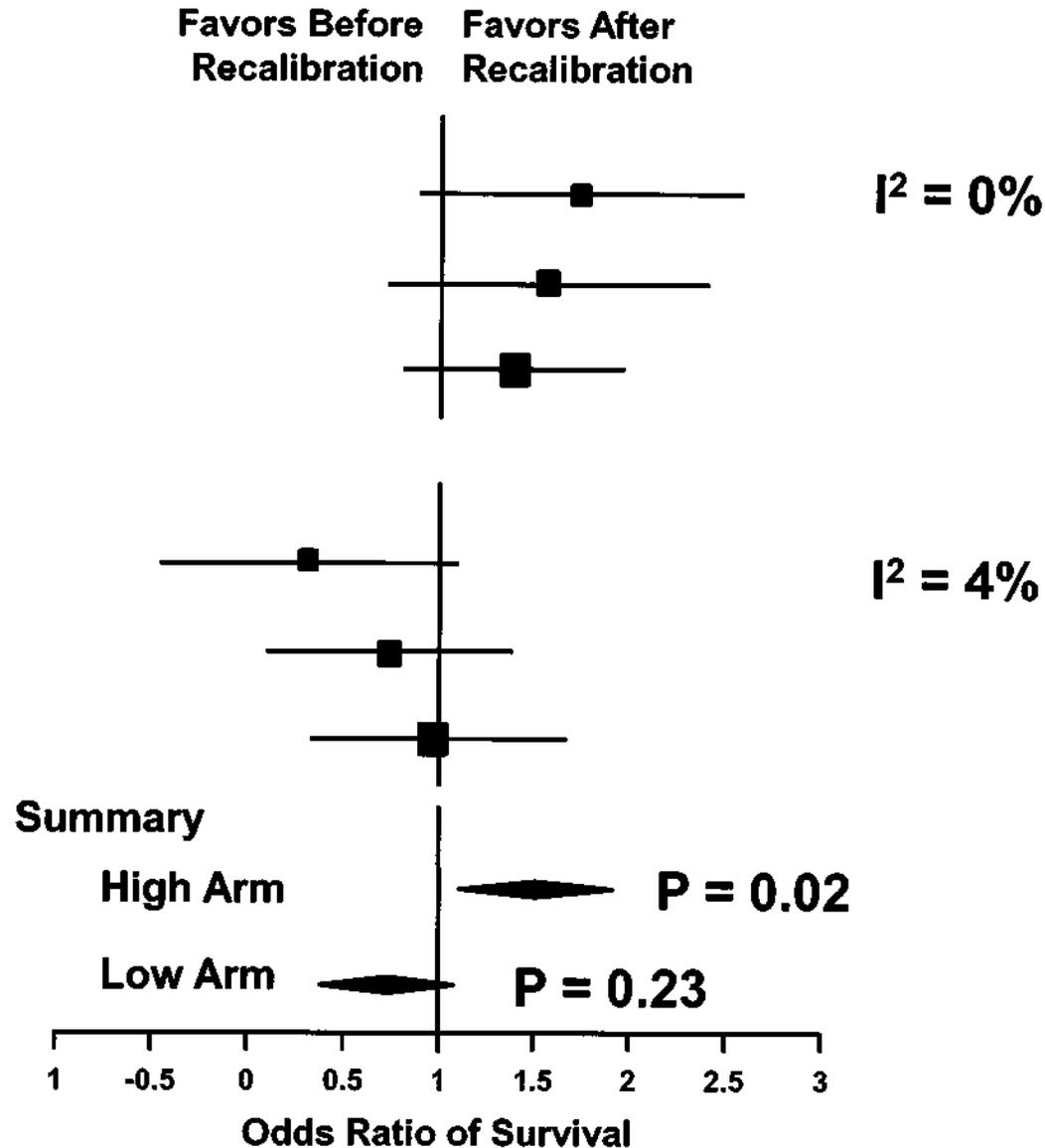
Canada

Low O<sup>2</sup> Saturation  
Range Arm (85-89%)

United Kingdom

Australia

Canada



# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

Treatment Arm

Favors Before Favours After

**Decreasing oxygen exposure worsened survival rates in neonates already receiving levels lower than usual care**

Low O<sup>2</sup> Saturation  
Range Arm (85-89%)

United Kingdom

Australia

Canada

Summary

High Arm

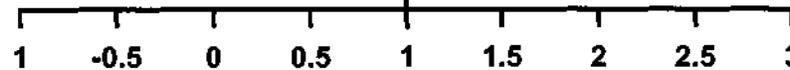
Low Arm

$I^2 = 4\%$

$P = 0.02$

$P = 0.23$

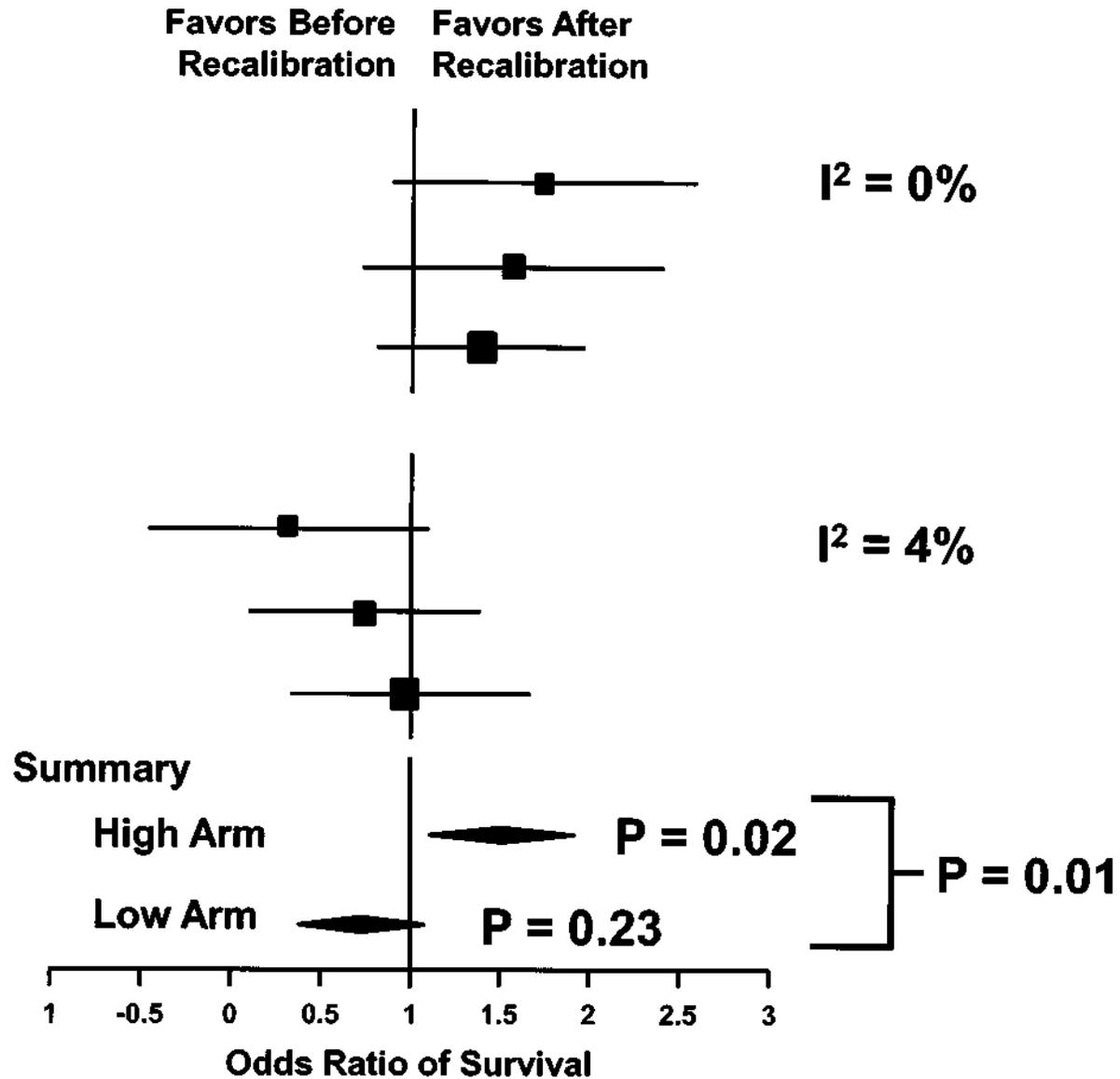
$P = 0.01$



Odds Ratio of Survival

# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

**Treatment Arm**  
**High O<sup>2</sup> Saturation**  
**Range Arm (91-95%)**  
United Kingdom  
Australia  
Canada  
**Low O<sup>2</sup> Saturation**  
**Range Arm (85-89%)**  
United Kingdom  
Australia  
Canada



# Effect on Survival by Treatment Group of Recalibration of Pulse Oximeters

**Treatment Arm**  
**High O<sup>2</sup> Saturation**  
**Range Arm (91-95%)**  
**United Kingdom**  
**Australia**

**Favors Before**   **Favors After**  
**Recalibration**   **Recalibration**



**The effects of lowering oxygen exposure on survival were significantly different and opposite, comparing the low and high oxygen target ranges**

**Canada**

**Summary**

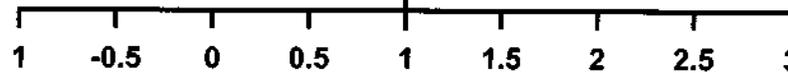
**High Arm**

**P = 0.02**

**Low Arm**

**P = 0.23**

**P = 0.01**



**Odds Ratio of Survival**

# Conclusions

- **Randomizing the critically ill to extremes of titrated therapies creates practice misalignments which carry risks and do not represent usual care**
- **A usual care control arm is essential to adequately monitor safety and inform practice**

**From:** [Finer, Neil](#)  
**To:** [Tyson, Jon E](#); [Wally Carlo, M.D.](#); [Walsh, Michele](#)  
**Cc:** [Abhik Das \(Adas@rti.org\)](#) ([Adas@rti.org](#)); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kennedy, Kathleen A](#)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Friday, November 22, 2013 3:39:16 PM

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I would support such analyses being completed and published  
Neil

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**From:** [Tyson, Jon E \[mailto:Jon.E.Tyson@uth.tmc.edu\]](#)  
**Sent:** Friday, November 22, 2013 8:00 PM  
**To:** [Wally Carlo, M.D.](#); [Walsh, Michele](#); [Finer, Neil](#)  
**Cc:** [Abhik Das \(Adas@rti.org\)](#) ([Adas@rti.org](#)); [Rose Higgins MD \(higginsr@mail.nih.gov\)](#); [Kennedy, Kathleen A](#)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Do you and the committee want to discuss whether it might be feasible and desirable to do analyses restricted to infants alive at 24 hrs and compare the 3 studies with respect to 1) the "true" oxygen saturation distribution to 36 wks by saturation group; 2) RR for death for low vs. high sat goal identified from regression equations that included as predictor variables treatment group and center; and 3) RR for death for low and high oxygen sat group adjusted for center, treatment group, and a few other variables, perhaps gestational age, FO2 at 24 h (or at close to it as possible), and vent support (yes, no or MAP if available)?

More simply, the committee could also consider doing an additional analysis restricted to SUPPORT with infants classified according to severity of illness at or near enrollment (high or lower based on first FiO2 x MAP) and assess whether there is evidence of a treatment x severity of illness interaction on the RR for death with low vs high sat goals. Evidence that the effect of the saturation goal in the sickest infants differed from that in less sick infants might help explain the differences between studies and might be a reasonable analysis to do even if the studies had altogether similar results.

As Wally and I discussed and as I said in my e mail, he may well be correct that these differences between studies in the findings may all due to the play of chance. There are some differences from the trials with antenatal steroid trials in 1) The variability across the antenatal steroid trials reflects the small size of the trials. (The largest trial the Liggins trial (n=1079), resulted in a risk difference virtually identical to that of the meta analysis. The average number of total patients in the other trials was only 180 patients, much smaller than BOOST, COT, and SUPPORT; and 2) the meta-analysis of the antenatal steroid trials didn't identify evidence of a heterogeneous treatment effect whereas there may be a treatment x algorithm interaction in a proper meta-analysis of the saturation trials that in contrast to the steroid meta-analysis might make it difficult to come up with a meaningful overall effect size.

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**From:** [Wally Carlo, M.D. \[mailto:WCarlo@peds.uab.edu\]](#)  
**Sent:** Wednesday, November 20, 2013 12:59 PM  
**To:** [Walsh, Michele](#); [Finer, Neil](#); [Tyson, Jon E](#)

**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Michele and Neil:

You raise important points. I agree it is difficult to try to use comparisons of saturation data to argue the results of 5 trials and almost 5000 babies.

This is reminiscent of the antenatal steroids controversies which delayed ramping up antenatal steroids treatment for decades.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
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176F Suite 9380R  
Birmingham, AL 35233-7335  
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FAX: 205 934 3100  
Cell: (b)(6)

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**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Wednesday, November 20, 2013 6:57 AM  
**To:** Finer, Neil; Wally Carlo, M.D.; Tyson, Jon E [[Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu)]  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Jon: Your points are well taken.  
This will be the topic of a (I am sure) lively debate at Hot Topics.  
I think the early enrollment in a period of instability may have greatly influenced the findings- has there ever been an analysis showing saturation excluding those who died in the first 24 hours- what impact of those on the median and tail?  
Another difference in addition to those Neil cited: BOOST and COT collected detailed saturation data only during the first 2 weeks- after there are only snapshots, I believe for one day weekly, when the baby was in oxygen for > 12 hours.  
Finally COT continued on the study oximeter until discharge even if in RA. SUPPORT and BOOST reverted to non-study oximeter when out of oxygen or at 36 weeks. So it is not clear to me that the saturation data are at all comparable.

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**From:** Finer, Neil [[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)]  
**Sent:** Wednesday, November 20, 2013 1:24 AM  
**To:** Tyson, Jon E; Wally Carlo, M.D.; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Frantz, Ivan; ([EMcGowan@tufts-nemc.org](mailto:EMcGowan@tufts-nemc.org)); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); ([suhas.kallapur@cchmc.org](mailto:suhas.kallapur@cchmc.org)); Abbot Laptook ([alaptook@wihri.org](mailto:alaptook@wihri.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Ambal ([ambal@uab.edu](mailto:ambal@uab.edu)); Anna Maria Hibbs

([AnnaMaria.hibbs@cwru.edu](mailto:AnnaMaria.hibbs@cwru.edu)); [barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu); [bpointex@iupui.edu](mailto:bpointex@iupui.edu); [carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu); Carlton, David P; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); [dwallace@rti.org](mailto:dwallace@rti.org); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Greg Sokol ([gsokol@iupui.edu](mailto:gsokol@iupui.edu)); Haresh Kirpalani ([KIRPALANI@email.chop.edu](mailto:KIRPALANI@email.chop.edu)); John Barks; Kennedy, Kathleen A; Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); Kurt Schibler [[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)]; Luc Brion ([luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)); Martin Keszler ([mkeszler@wihri.org](mailto:mkeszler@wihri.org)); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu); Meena Garg ([mgarg@mednet.ucla.edu](mailto:mgarg@mednet.ucla.edu)); Nelin, Leif; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Polin, Richard; Robin Ohls ([rohls@salud.unm.edu](mailto:rohls@salud.unm.edu)); [ronnie\\_guillet@urmc.rochester.edu](mailto:ronnie_guillet@urmc.rochester.edu); Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [[bsood@med.wayne.edu](mailto:bsood@med.wayne.edu)]; Truog, William (MD); Uday Devaskar ([UDEVASKAR@MEDNET.UCLA.EDU](mailto:UDEVASKAR@MEDNET.UCLA.EDU)); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu))

**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Hi Jon

This is a very thoughtful review

We need to remember a few differences between the trials

SUPPORT enrolled essentially all comers into both arms, and there were 2 interventions, and this enrollment occurred at birth and by 2 hours for the actual oximeter placement

In fact all were enrolled at birth and we excluded no infant after that

What that means however is not as obvious

The other trials had up to 18-24 hours and excluded infants who were unstable etc

BOOST excluded infants if they were thought unlikely to survive or to be available for follow-up

COT excluded 182 infants not considered viable and a further 80 with pulmonary hypertension and 205 not thought to be available for follow-up

The results of this are likely seen in the Medians etc for actual SpO2

We had there are 13 infants (5 in the low target group and 8 in the high target group) with median oxygen saturations below 80%.

All of these infants died within the first two days of life, 10 on day 1, and the number of hours of oximeter data for each infant is limited: median 6.8 hours, IQR 4.4-13.2 hours, range 0.6-41.2 hours.

These infants contribute to the low medians and our tail in that direction and they all died. None would have been enrolled in the other trials. This may represent the tip of the iceberg in terms of differences in outcome. Perhaps maintaining lower vs higher SpO2 on day 1 is critical. The plausibility for this comes from the DR data regarding room air vs oxygen for the tem infant- in this situation only minutes of oxygen exposure made a difference

Day 1 represents a very unstable period

In addition for sites that used the new algorithm, did they have a new conversion algorithm for the calculation of the actual sat from the recorded sat?

We would not know because we did not have any oximeters with the new algorithm

In the original algorithm, as the SpO2 values move toward 85% there are a number of read values that will not correspond to an actual individual real value

This also occurs on the high end

In addition this could result in the changes in read SpO2 occurring somewhat quicker

We did not believe that any caretakers were unblinded by these changes, but did they respond in the same fashion using both hi and low oximeters?

I wondered whether the changes to the new algorithm were associated with increased or different vigilance by the care teams

The PI'S don't think so, and if I recall Barbara said that they did not know when this change was made

I believe that all sites used the same information to revert to normal values from read/stored values but I can't be certain that in their actual analyses this was done

I do not know, as I said earlier if they used a different conversion scheme when they changed calibration algorithms

Finally while we did not see an interaction between our 2 interventions, could there have been an effect of our protocolized care for the infants ( CPAP vs Surf) that affected our observations and results

We did give surf in the first 1 hour to more than 50% of these infants, and this is also not replicated in the other trials

At this point, I think all your suggestions are reasonable and we should remember that our study was quite different and much more complex

In addition perhaps this is a reason that the other studies could have spent more time educating their caretakers to keep the babies in a tighter range, while our teams had a complete respiratory protocol to follow

More questions than answers

Neil

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Wednesday, November 20, 2013 12:43 AM

**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; Finer, Neil; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale\_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpointindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wcarlo@uab.edu); Finer, Neil

**Subject:** Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

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To summarize, with the original algorithm, mortality with the lower saturation goal was significantly increased in SUPPORT (RR = 1.27 [1.01-1.60]; n =1316, all with the original algorithm). In contrast, there was no evidence of increased death with use of allegedly the same algorithm in either the first phase of BOOST II (RR =0.90 [0.70-1.15]; n=1259) or in the first phase of COT (OR = 1.00 (0.63-1.59 [adjusted for center, as appropriate in SUPPORT; total n =549). With the results in SUPPORT being just barely significant, a meta-analysis of these results with the original algorithm would clearly not be significant. While this finding ultimately could be good news that might possibly be of use in defending

ourselves against the Public Citizen law suit, the data become more confusing in comparing the findings for mortality before and after installing the revised algorithm.

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Shouldn't these results should make us concerned about the possibility that more than what we understand changed between the first and revised algorithm? This concern prompts the following kind of questions about SUPPORT that that I don't recall were addressed previously (though perhaps at a Steering Committee I missed –if so, I apologize for raising any questions that have already been well addressed.)

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3. In SUPPORT and COT, the oxygen saturations curves are display in terms of the median saturations for individual infants. Median values of course do not indicate the proportion of time that infants had extreme value. It is hard to compare the studies with respect to the proportion of

time that infants spent at different saturation values in the different studies. This is important to understanding whether the mortality differences reflect differences in the % of time spent at very low (or possibly even very high) saturations. Abhik can you send (or if I missed it, please resend) figures for SUPPORT constructed like those in BOOST II Figure 1 showing percent of time spent at different saturations as a % of total time receiving oxygen.

4. Ref the generalizability of SUPPORT findings to current practice, has Massimo indicated that the values displayed on oximeters now in use are identical to what would the ones calculated as the "actual" value with both the original and revised algorithms in the different trials and hasn't been tinkered with again?

The BOOST investigators note: "In conclusion, preterm infants born before 28 weeks' gestation with a target oxygen saturation of 85 to 89% had a significantly higher rate of death than did those with a target of 91 to 95% in a subgroup *whose treatment involved an oximeter-calibration algorithm similar to that in current use*" [italics mine]. It bothers me that the words aren't "...identical to that in current use," Does this bother anyone but me?

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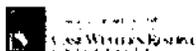
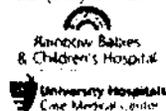
**From:** [Walsh, Michele](#)  
**To:** [Wally Carlo, M.D.](#); [Tyson, Jon E](#); [Finer, Neil](#)  
**Cc:** [Abhik Das \(Adas@rti.org\)](#) ([Adas@rti.org](#)); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kennedy, Kathleen A](#)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Friday, November 22, 2013 2:31:51 PM

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We also have the secondary by episodes of Intermittent Hypoxia which is back into study section.

*Michele Walsh*

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**Professor of Pediatrics**  
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**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Friday, November 22, 2013 2:25 PM  
**To:** Tyson, Jon E; Walsh, Michele; Finer, Neil  
**Cc:** Abhik Das ([Adas@rti.org](mailto:Adas@rti.org)) ([Adas@rti.org](mailto:Adas@rti.org)); Rose Higgins MD ([higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)); Kennedy, Kathleen A  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Jon:

We have a protocol for this secondary analysis. I think I will have to draft a revised protocol before more analyses can be done other than the minor request on how to display the data by mean sats rather than medians.

What you are suggesting is largely a major revision of the protocol that I believe requires a lot of thought and may not be appropriate.

As I mentioned to you in the call, I have a grant application submitted to work with the three data bases, not just SUPPORT. I have been working with Ben Stenson on O2 sats analyses. I think it would be best to coordinate and think this more carefully before we jump into multiple analyses.

Wally

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**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Friday, November 22, 2013 1:00 PM  
**To:** Wally Carlo, M.D.; Walsh, Michele; Finer, Neil  
**Cc:** Abhik Das ([Adas@rti.org](mailto:Adas@rti.org)) ([Adas@rti.org](mailto:Adas@rti.org)); Rose Higgins MD ([higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)); Kennedy, Kathleen A

**Subject: RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?**

Do you and the committee want to discuss whether it might be feasible and desirable to do analyses restricted to infants alive at 24 hrs and compare the 3 studies with respect to 1) the "true" oxygen saturation distribution to 36 wks by saturation group ; 2) RR for death for low vs. high sat goal identified from regression equations that included as predictor variables treatment group and center; and 3) RR for death for low and high oxygen sat group adjusted for center, treatment group, and a few other variables, perhaps gestational age, FO2 at 24 h (or at close to it as possible), and vent support (yes, no or MAP if available)?

More simply, the committee could also consider doing an additional analysis restricted to SUPPORT with infants classified according to severity of illness at or near enrollment (high or lower based on first FiO2 x MAP ) and assess whether there is evidence of a treatment x severity of illness interaction on the RR for death with low vs high sat goals. Evidence that the effect of the saturation goal in the sickest infants differed from that in less sick infants might help explain the differences between studies and might be a reasonable analysis to do even if the studies had altogether similar results.

As Wally and I discussed and as I said in my e mail, he may well be correct that these differences between studies in the findings may all due to the play of chance. There are some differences from the trials with antenatal steroid trials in 1) The variability across the antenatal steroid trials reflects the small size of the trials. (The largest trial the Liggins trial (n=1079), resulted in a risk difference virtually identical to that of the meta analysis. The average number of total patients in the other trials was only 180 patients, much smaller than BOOST, COT, and SUPPORT; and 2) the meta-analysis of the antenatal steroid trials didn't identify evidence of a heterogeneous treatment effect whereas there may be a treatment x algorithm interaction in a proper meta-analysis of the saturation trials that in contrast to the steroid meta-analysis might make it difficult to come up with a meaningful overall effect size.

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**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]

**Sent:** Wednesday, November 20, 2013 12:59 PM

**To:** Walsh, Michele; Finer, Neil; Tyson, Jon E

**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Michele and Neil:

You raise important points. I agree it is difficult to try to use comparisons of saturation data to argue the results of 5 trials and almost 5000 babies.

This is reminiscent of the antenatal steroids controversies which delayed ramping up antenatal steroids treatment for decades.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
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176F Suite 9380R  
Birmingham, AL 35233-7335  
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Cell: (b)(6)

**From:** Walsh, Michele [mailto:Michele.Walsh@Uhhospitals.org]  
**Sent:** Wednesday, November 20, 2013 6:57 AM  
**To:** Finer, Neil; Wally Carlo, M.D.; Tyson, Jon E [Jon.E.Tyson@uth.tmc.edu]  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Jon: Your points are well taken.  
This will be the topic of a (I am sure) lively debate at Hot Topics.  
I think the early enrollment in a period of instability may have greatly influenced the findings- has there ever been an analysis showing saturation excluding those who died in the first 24 hours- what impact of those on the median and tail?  
Another difference in addition to those Neil cited: BOOST and COT collected detailed saturation data only during the first 2 weeks- after there are only snapshots, I believe for one day weekly, when the baby was in oxygen for > 12 hours.  
Finally COT continued on the study oximeter until discharge even if in RA. SUPPORT and BOOST reverted to non-study oximeter when out of oxygen or at 36 weeks. So it is not clear to me that the saturation data are at all comparable.

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**From:** Finer, Neil [nfiner@ucsd.edu]  
**Sent:** Wednesday, November 20, 2013 1:24 AM  
**To:** Tyson, Jon E; Wally Carlo, M.D.; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); dale\_phelps@urmc.rochester.edu; Frantz, Ivan; (EMcGowan@tufts-nemc.org); 'Duara, Shahnaz' (SDuara@med.miami.edu); moshea@wfubmc.edu; (sahas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpointindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Hi Jon

This is a very thoughtful review

We need to remember a few differences between the trials  
SUPPORT enrolled essentially all comers into both arms, and there were 2 interventions, and this enrollment occurred at birth and by 2 hours for the actual oximeter placement  
In fact all were enrolled at birth and we excluded no infant after that  
What that means however is not as obvious  
The other trials had up to 18-24 hours and excluded infants who were unstable etc  
BOOST excluded infants if they were thought unlikely to survive or to be available for follow-up  
COT excluded 182 infants not considered viable and a further 80 with pulmonary hypertension and 205 not thought to be available for follow-up  
The results of this are likely seen in the Medians etc for actual SpO<sub>2</sub>  
We had there are 13 infants (5 in the low target group and 8 in the high target group) with median oxygen saturations below 80%.  
All of these infants died within the first two days of life, 10 on day 1, and the number of hours of oximeter data for each infant is limited: median 6.8 hours, IQR 4.4-13.2 hours, range 0.6-41.2 hours. These infants contribute to the low medians and our tail in that direction and they all died. None would have been enrolled in the other trials. This may represent the tip of the iceberg in terms of differences in outcome. Perhaps maintaining lower vs higher SpO<sub>2</sub> on day 1 is critical. The plausibility for this comes from the DR data regarding room air vs oxygen for the term infant- in this situation only minutes of oxygen exposure made a difference  
Day 1 represents a very unstable period  
In addition for sites that used the new algorithm, did they have a new conversion algorithm for the calculation of the actual sat from the recorded sat?  
We would not know because we did not have any oximeters with the new algorithm  
In the original algorithm, as the SpO<sub>2</sub> values move toward 85% there are a number of read values that will not correspond to an actual individual real value  
This also occurs on the high end  
In addition this could result in the changes in read SpO<sub>2</sub> occurring somewhat quicker  
We did not believe that any caretakers were unblinded by these changes, but did they respond in the same fashion using both hi and low oximeters?  
I wondered whether the changes to the new algorithm were associated with increased or different vigilance by the care teams  
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More questions than answers

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**Sent:** Wednesday, November 20, 2013 12:43 AM

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2. How can we be certain that the method used to calculate TRUE saturation curves (what we call the "actual" saturation values in the SUPPORT figure 3) are correct and the same as in BOOST and COT when the original algorithm was used? Is there a way independent of the company to determine this?

According to the BOOST investigators noted (as stated bottom of left hand column to top of right hand column on page 2097) that "Displayed oxygen-saturation values *gradually reverted to actual values* when the measured value was outside the range of 85 to 95%." [italics mine]. In SUPPORT (1<sup>st</sup> column of page 1962), we note oxygen saturation "...reverted to actual (nonskewed) values when it was less than 84% or higher than 96%.." ( The same is noted for COT.) Might the subtle difference in wording reflect a subtle but important difference (or perhaps even a sizable unintended difference) in the actual algorithm or the method to calculate the true saturation values?

3. In SUPPORT and COT, the oxygen saturations curves are display in terms of the median saturations for individual infants. Median values of course do not indicate the proportion of time that infants had extreme value. It is hard to compare the studies with respect to the proportion of time that infants spent at different saturation values in the different studies. This is important to understanding whether the mortality differences reflect differences in the % of time spent at very low (or possibly even very high) saturations. Abhik can you send (or if I missed it, please resend) figures for SUPPORT constructed like those in BOOST II Figure 1 showing percent of time spent at different saturations as a % of total time receiving oxygen.

4. Ref the generalizability of SUPPORT findings to current practice, has Massimo indicated that the values displayed on oximeters now in use are identical to what would the ones calculated as the "actual" value with both the original and revised algorithms in the different trials and hasn't been tinkered with again?

The BOOST investigators note: "In conclusion, preterm infants born before 28 weeks' gestation with a target oxygen saturation of 85 to 89% had a significantly higher rate of death than did those with a target of 91 to 95% in a subgroup *whose treatment involved an oximeter-calibration algorithm similar to that in current use*" [italics mine]. It bothers me that the words aren't "...identical to that in current use," Does

this bother anyone but me?

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**Subject:** FW: Janvier's commentary  
**Date:** Friday, November 22, 2013 11:11:53 AM  
**Attachments:** Janvier's commentary.pdf

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The American journal of Bioethics has an entire issue devoted to the SUPPORT Trial – see the note and article below from Dr. Janvier.

Rose

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**Subject:** Janvier's commentary

**See the attached commentary by Annie Janvier. Have a great weekend.**

**Wally**

**From:** annie janvier [mailto:(b)(6)@hotmail.com]  
**Sent:** Friday, November 22, 2013 8:17 AM  
**To:** edward bell iowa; Wally Carlo, M.D.; neil finer; PAS O Shea  
**Subject:** support trial, my comment

the AJ of Bioethics just published some articles about Support and there are a couple of commentaries.

This saga with support has bothered me as a neonatologist, even more as an ethicist (bad press for ethicists in my opinion, many displays of mediocre thinking) but has really hurt me as a parent to see how one could quickly sabotage great research initiatives done by those who care.

I wrote one of of the articles.

<http://www.ncbi.nlm.nih.gov/pubmed/24256537>

I just want all of the SUPPORT investigators to know that my heart goes to researchers like you.

Without people like you, (b)(6)

Annie

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### In Support of SUPPORT: Ignorance and Mistrust Can Harm Babies and Families

Annie Janvier<sup>a</sup>

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# In Support of SUPPORT: Ignorance and Mistrust Can Harm Babies and Families

Annie Janvier, University of Montreal and Sainte-Justine Hospital

I am a neonatologist, a clinical investigator, and a clinical ethicist. I am also the mother of Violette, who was born at 24 weeks of gestational age. Violette participated in many clinical trials. We did not consent to trials because we are researchers. We did not consent to the trials altruistically out of a desire to help others. We consented because we are Violette's parents and we love her. We know enough about trials to know that the outcomes for babies are often better when they are in research projects than when they are not (Vist et al. 2008).

It is troubling that many critics of SUPPORT, including Macklin and colleagues, don't seem to have spent any time in an neonatal intensive care unit (NICU), enquired about NICU protocols, or observed communication between neonatologists and parents. They don't seem to understand either routine NICU care or what it means to be in a large clinical trial in neonatology (Macklin et al. 2013a; 2013b; 2013c).

The Canadian Oxygen Trial had not started when Violette was born. If it had been, Violette would have been enrolled. At that time, if I'd had a choice, I would have chosen the low saturation group, using my gut feeling. I would have been wrong. I am grateful that clinical investigators have recognized and acknowledged that our clinical judgments and "doing what we think standard of care should be" are often wrong. Babies and their parents deserve more. When scholars proclaim that "Recognition of the investigator-physician conflict of interest runs long and deep and while yet poorly managed, we cannot ignore it. But it is . . . the doctors, and not the researchers, who have a fiduciary obligation and long-standing ethic to pursue the patient's best interests above all other considerations," it demonstrates that they do not understand in what context large neonatal clinical trials are being done.

When actors play the role of doctors or parents, they spend months in a hospital. Medical anthropologists and journalists who report on neonatal outcomes also spend a considerable amount of time in NICUs. It is a shame this strive for excellence is not universally present for scholars in bioethics, who are in privileged and important positions. Had they been present for a significant amount of time in an NICU with any of the SUPPORT trial investigators, they would have learned valuable things. They would have noted that clinical investigators in NICUs are neonatologists whose experience has taught them how often neonatologists have been wrong in their deeply held beliefs. They might have understood that in the intensive care world, "normal"

values (PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, BP, hemoglobin, etc.) have often been proved harmful; this has led intensivists to do less intervention: fewer intubations, less surfactant, fewer central lines, less antibiotics, fewer transfusions, fewer surgeries, and so on. This "gentler care" has improved outcomes.

The bioethics scholars could have observed how neonatologists interact with parents. They would have seen how tiny a preterm infant is, how the pulse oximeter is twice as big as she is. They would have been exposed to NICU protocols: Personalized care implies titrating the oxygen for each baby using protocols, not by having different oxygen targets for different babies. They would have observed how both parents and doctors are obsessed with oxygen saturation numbers, with alarms constantly ringing. They would have also seen babies die, how they become mottled and purple; and their parents holding them, alternating between bouts of crying that sometimes look like seizures and moments of immobility and emptiness. They would have seen a neonatologist in the room, sometimes holding a mother's hand, other times being present at the baptism. As a neonatologist (and a clinical investigator), I feel intense loyalty to my patients. I show that loyalty by telling patients what we know and what we don't know. We are loyal first to the babies, not to the research study. We share a commitment to improving outcomes for babies by treating each baby to the best of our ability. That sometimes means enrolling babies in well-designed research projects.

The SUPPORT trial could have been conducted using different strategies: (1) Waiver of consent: This has the advantage of being less costly (less money going for nonparticipants and research question answered quicker) and truly representative (Rich et al. 2012) but the disadvantage of not being considered "ethical" by many. (2) Thorough informed consent: This has the advantage that an irreproachable "ethical" approach to research is being used but the disadvantage of not being as representative (Rich et al. 2012) and much more costly. (3) Opt-out approach: This option could have had the advantages of both previously mentioned approaches. As a parent who has experienced a delivery at 24 weeks and the ups and downs of the NICU, I would favor the opt-out approach. As a neonatologist, I would favor the same. As a researcher, I would choose thorough informed consent to protect myself and my institution. This is the only item where I think differently as a neonatologist than as a clinical investigator. There are now so many safeguards to conduct neonatal research that I wonder whether we are protecting hospitals or patients. Are we are trying

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to satisfy “The Law,” “The Ethicists,” and “The IRB,” more than parental needs? How do parents of preterm infants want their babies to be protected? Which do they fear most: research or nonvalidated therapy? We are faced with the opinions of those who think about these issues, and the opinions of those who speak to these parents every day and also think about these issues. Amazingly, nobody has investigated the opinion of the parents!

SUPPORT has attracted more attention than many other trials. I suspect that one of the reasons is because it involves oxygen. Oxygen is not like other interventions. Oxygen has a psychological impact on individuals that other medications do not have: It is perceived as life. Some authors have compared the low-saturation arm to “asphyxia” or “choking” the babies. I think the study would not have been nearly as controversial if the excess mortality happened in the “high-saturation arm.”

Clinical researchers understand the need for regulation and oversight. These prevent individuals from causing harm to patients by doing dangerous and rash things. Institutional review boards and government regulations insure the safety of vulnerable patients. Many unethical researchers have abused patients. There were no laws about research in the past. Since then, a plethora of protections have been implemented. The pendulum has shifted drastically. In this controversy, we’ve seen that reckless ethical speculation by people who don’t understand neonatology or clinical research can also be harmful. In this controversy, one has to wonder where the conflicts of interest lie. Academic ethicists seem oblivious to their own “divided loyalties.” Their primary source of income is not through clinical care. They need visibility. Academic ethicists advance their careers by creating controversies. These garner them invitations to speak at conferences, write articles, and obtain grants. If they demonstrate that clinical investigators have conflicted interests and need additional guidance to

ethically lead research, they are generating employment prospects.

Academic ethicists have realized that they can paralyze research. With this power comes the duty to excel. This demands collaboration and trust in clinical investigators; this demands humility and curiosity. To suggest that clinician-investigators have divided loyalties and sometimes feel a conflict between what is good for a baby and what is good for a study is a serious charge. It alters the trust parents have in the medical system when they are the most vulnerable. It paralyzes further improvements in neonatal care. The consequences of a bad film or bad anthropological research do not have the negative impact mediocre articles in research ethics have. Perhaps it is time to regulate the regulators. ■

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## Community Engagement: Critical to Continued Public Trust in Research

Emily E. Anderson, Loyola University of Chicago  
Stephanie Solomon, Saint Louis University

The three target articles in this issue focus on flaws in the informed consent process in the SUPPORT study and the need for perhaps different standards of disclosure for research involving treatments that are already available (or “standard of care” treatments). Echoing the recent groundswell of support for community-engaged and patient-centered research

(Institute of Medicine 2013), Wilfond (2013) raises the importance of engaging the public as “critical to interpreting federal policy for the protection of human subjects in ways that are acceptable to all and that further the public interest.” We enthusiastically agree, and would like to explore whether public engagement could have changed the course

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**From:** Das, Abhik  
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**Cc:** wacarlo@uab.edu; nfiner@ucsd.edu  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Wednesday, November 20, 2013 9:42:03 PM

---

Great, thanks for letting me know.  
Abhik

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

**From:** Tyson, Jon E [Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Wednesday, November 20, 2013 08:14 PM Eastern Standard Time  
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**Cc:** Das, Abhik; Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu); nfiner@ucsd.edu  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Thanks, Abhik, for sending analyses previously done by Marie.

I called Wally and had a long discussion that I very much appreciate. He indicated that a number of the analyses requested were already done and will indicate ones that haven't been done. More later.

---

**From:** Tyson, Jon E  
**Sent:** Wednesday, November 20, 2013 11:26 AM  
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**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Rose, as I would think the Steering Committee would agree, a separate proposal should be unnecessary. I understand the prior analyses were done by Marie without a separate proposal or without formal prior review and agreement by the subcommittee. Furthermore, RTI does lots of analyses at their discretion, as is appropriate and for many proposals, necessary when the specific analyses for secondary or even primary outcomes were not specified in the proposals. Likewise, RTI at their discretion or at the discretion of the subcommittee can run analyses of the kind suggested.

With the important, unexplained and conflicting results between multiple international trials using the same saturation targets, such analyses of the kind are clearly needed to better understand what may be the Network's most important trial. I raise my questions to the Steering Committee and the SUPPORT subcommittee to consider.

---

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**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to

understand the results and how they should be applied?

Jon

Can you send a proposal that the SUPPORT subcommittee can review? After discussion by the subcommittee, Marie Gantz had looked at some actual oxygen saturation data awhile ago. There is a huge amount of data as saturation recordings were done every 10 seconds. The updated proposal templates are at:

<https://neonatal.rti.org/index.cfm?fuseaction=administration.protocolreview>

Thanks

Rose

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**Sent:** Tuesday, November 19, 2013 6:43 PM

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**Subject:** Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

As Wally thinks, it may be that the differences in RR and OR for death in the different studies and in different phases of the same study are due to the play of chance and that with current technology and methods of care, the 85-89% saturation range will result in a higher overall mortality than the 91-95% sat range. However, on careful rereading of SUPPORT, BOOST, and COT, the findings seem very difficult to reconcile and worthy of detailed discussion and review of the findings.

To summarize, with the original algorithm, mortality with the lower saturation goal was significantly increased in SUPPORT (RR = 1.27 [1.01-1.60]; n =1316, all with the original algorithm). In contrast, there was no evidence of increased death with use of allegedly the same algorithm in either the first phase of BOOST II (RR =0.90 [0.70-1.15]; n=1259) or in the first phase of COT (OR = 1.00 (0.63-1.59 [adjusted for center, as appropriate in SUPPORT; total n =549). With the results in SUPPORT being just barely significant, a meta-analysis of these results with the original algorithm would clearly not be significant. While this finding ultimately could be good news that might possibly be of use in defending ourselves against the Public Citizen law suit, the data become more confusing in comparing the findings for mortality before and after installing the revised algorithm.

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**From:** [Wally Carlo, M.D.](#)  
**To:** [Tyson, Jon E; Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Abhik Das \(Adas@rti.org\) \(Adas@rti.org\)](#); [Wally Carlo \(wacarlo@uab.edu\) \(wacarlo@uab.edu\)](#); [nfiner@ucsd.edu](#)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Wednesday, November 20, 2013 1:57:53 PM

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Jon:

A few clarifications. There was a protocol to analyze O2 sats for mortality associations with specific hypotheses and an analysis plan that was approved. All proposed analyses and some exploratory analyses approved by the committee were performed. There were no significant associations.

The committee decided to focus on the ROP analysis, and that paper is in draft form.

I think we need to plan carefully any analysis.

Wally

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**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Wednesday, November 20, 2013 11:26 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** [Abhik Das \(Adas@rti.org\) \(Adas@rti.org\)](#); [Wally Carlo \(wacarlo@uab.edu\) \(wacarlo@uab.edu\)](#); [nfiner@ucsd.edu](#)  
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**Sent:** Wednesday, November 20, 2013 10:40 AM  
**To:** Tyson, Jon E  
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Thanks

Rose

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**Sent:** Tuesday, November 19, 2013 6:43 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Frantz, Ivan; ([EMcGowan@tufts-nemc.org](mailto:EMcGowan@tufts-nemc.org)); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); ([suhas.kallapur@cchmc.org](mailto:suhas.kallapur@cchmc.org)); Abbot Laptook ([alaptook@wihri.org](mailto:alaptook@wihri.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Ambal ([ambal@uab.edu](mailto:ambal@uab.edu)); Anna Maria Hibbs ([AnnaMaria.hibbs@cwru.edu](mailto:AnnaMaria.hibbs@cwru.edu)); [barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu); [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); [carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu); Carlton, David P; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); [dwallace@rti.org](mailto:dwallace@rti.org); Ed Bell ([edward-bell@iowa.edu](mailto:edward-bell@iowa.edu)); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Greg Sokol ([gsokol@iupui.edu](mailto:gsokol@iupui.edu)); Haresh Kirpalani ([KIRPALANI@email.chop.edu](mailto:KIRPALANI@email.chop.edu)); John Barks; Kennedy, Kathleen A; Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); Kurt Schibler [[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)]; Luc Brion ([luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)); Martin Keszler ([mkeszler@wihri.org](mailto:mkeszler@wihri.org)); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu); Meena Garg ([mgarg@mednet.ucla.edu](mailto:mgarg@mednet.ucla.edu)); Nelin, Leif; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Polin, Richard; Robin Ohls ([rohls@salud.unm.edu](mailto:rohls@salud.unm.edu)); [ronnie\\_guillet@urmc.rochester.edu](mailto:ronnie_guillet@urmc.rochester.edu); Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [[bsood@med.wayne.edu](mailto:bsood@med.wayne.edu)]; Truog, William (MD); Uday Devaskar ([UDEVASKAR@MEDNET.UCLA.EDU](mailto:UDEVASKAR@MEDNET.UCLA.EDU)); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
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**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Wednesday, November 20, 2013 12:33:54 PM

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I don't quite agree with Jon's characterization of our work. We don't do anything unless directed by the subcommittee, trial PI, NIH or the DSMC, unless it is narrowly related to data cleaning issues.

Thanks

Abhik

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Wednesday, November 20, 2013 12:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik; Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu); nfiner@ucsd.edu  
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**Sent:** Wednesday, November 20, 2013 10:40 AM  
**To:** Tyson, Jon E  
**Cc:** Abhik Das (adas@rti.org); 'Wally Carlo, M.D.'; nfiner@ucsd.edu  
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The saturation distributions would be derived from a very large number of observations in BOOST and in SUPPORT. If the same bimodal distribution is not present in BOOST and SUPPORT, we need to dig further order to better understand the differences between the studies and be convinced that the "original" algorithms were in fact identical. Ref COT, it is hard to discern (at least to my eyes) from the data presented in the manuscript or appendix whether a bimodal distribution occurred in that study similar to that in BOOST; we might want to ask if the COT investigators can provide such curves from what they collected, particularly if our distributions differ from those in BOOST. As I understand it, the bimodal distribution is the expected result of the algorithm itself (the reason Massimo revised it in response to the findings in BOOST) rather than the way NICU staff used the oximeters to adjust FIO<sub>2</sub>, right? If so, the absence of a bimodal distribution in either COT or SUPPORT would prompt further worry that the "original" algorithm was not exactly the same in SUPPORT, COT, and BOOST II.

2. How can we be certain that the method used to calculate TRUE saturation curves (what we call the "actual" saturation values in the SUPPORT figure 3) are correct and the same as in BOOST and COT when the original algorithm was used? Is there a way independent of the company to determine this?

According to the BOOST investigators noted (as stated bottom of left hand column to top of right hand column on page 2097) that "Displayed oxygen-saturation values *gradually reverted to actual values* when the measured value was outside the range of 85 to 95%." [italics mine]. In SUPPORT (1<sup>st</sup> column of page 1962), we note oxygen saturation "...reverted to actual (nonskewed) values when it was less than 84% or higher than 96%.." ( The same is noted for COT.) Might the subtle difference in wording reflect a subtle but important difference (or perhaps even a sizable unintended difference) in the actual algorithm or the method to calculate the true saturation values?

3. In SUPPORT and COT, the oxygen saturations curves are display in terms of the median saturations for individual infants. Median values of course do not indicate the proportion of time that infants had extreme value. It is hard to compare the studies with respect to the proportion of time that infants spent at different saturation values in the different studies. This is important to understanding whether the mortality differences reflect differences in the % of time spent at very low (or possibly even very high) saturations. Abhik can you send (or if I missed it, please resend) figures for SUPPORT constructed like those in BOOST II Figure 1 showing percent of time spent at different saturations as a % of total time receiving oxygen.

4. Ref the generalizability of SUPPORT findings to current practice, has Massimo indicated that the values displayed on oximeters now in use are identical to what would the ones calculated as the "actual" value with both the original and revised algorithms in the different trials and hasn't been tinkered with again?

The BOOST investigators note: "In conclusion, preterm infants born before 28 weeks' gestation with a target oxygen saturation of 85 to 89% had a significantly higher rate of death than did those with a target of 91 to 95% in a subgroup *whose treatment involved an oximeter-calibration algorithm similar to that in current use*" [italics mine]. It bothers me that the words aren't "...identical to that in current use," Does this bother anyone but me?

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?  
**Date:** Wednesday, November 20, 2013 12:30:55 PM

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That may be ok, but it is sometimes just too big a group to have a thoughtful discussion. My preference would be a subcommittee discussion, but I will go with whatever you decide. You may want to chat with Neil and Wally as well.

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, November 20, 2013 12:27 PM  
**To:** Das, Abhik  
**Subject:** FW: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Abhik

How about we discuss on the Tuesday SC call??

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Wednesday, November 20, 2013 12:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Abhik Das ([Adas@rti.org](mailto:Adas@rti.org)) ([Adas@rti.org](mailto:Adas@rti.org)); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)) ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Rose, as I would think the Steering Committee would agree, a separate proposal should be unnecessary. I understand the prior analyses were done by Marie without a separate proposal or without formal prior review and agreement by the subcommittee. Furthermore, RTI does lots of analyses at their discretion, as is appropriate and for many proposals, necessary when the specific

analyses for secondary or even primary outcomes were not specified in the proposals. Likewise, RTI at their discretion or at the discretion of the subcommittee can run analyses of the kind suggested.

With the important, unexplained and conflicting results between multiple international trials using the same saturation targets, such analyses of the kind are clearly needed to better understand what may be the Network's most important trial. I raise my questions to the Steering Committee and the SUPPORT subcommittee to consider.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wednesday, November 20, 2013 10:40 AM  
**To:** Tyson, Jon E  
**Cc:** Abhik Das ([adas@rti.org](mailto:adas@rti.org)); 'Wally Carlo, M.D.'; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** RE: Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

Jon

Can you send a proposal that the SUPPORT subcommittee can review? After discussion by the subcommittee, Marie Gantz had looked at some actual oxygen saturation data awhile ago. There is a huge amount of data as saturation recordings were done every 10 seconds. The updated proposal templates are at:

<https://neonatal.rti.org/index.cfm?fuseaction=administration.protocolreview>

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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6100 Executive Blvd., Room 4B03  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Tuesday, November 19, 2013 6:43 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); [dale\\_phelps@umc.rochester.edu](mailto:dale_phelps@umc.rochester.edu); Frantz, Ivan; ([EMcGowan@tufts-nemc.org](mailto:EMcGowan@tufts-nemc.org)); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); ([suhas.kallapur@cchmc.org](mailto:suhas.kallapur@cchmc.org)); Abbot Laptook ([alaptook@wihri.org](mailto:alaptook@wihri.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Ambal ([ambal@uab.edu](mailto:ambal@uab.edu)); Anna Maria Hibbs ([AnnaMaria.hibbs@cwru.edu](mailto:AnnaMaria.hibbs@cwru.edu)); [barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu); [bpointex@iupui.edu](mailto:bpointex@iupui.edu); [carl\\_dangio@umc.rochester.edu](mailto:carl_dangio@umc.rochester.edu); Carlton, David P; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); [dwallace@rti.org](mailto:dwallace@rti.org); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Greg Sokol ([gsokol@iupui.edu](mailto:gsokol@iupui.edu)); Haresh Kirpalani ([KIRPALANI@email.chop.edu](mailto:KIRPALANI@email.chop.edu)); John Barks; Kennedy, Kathleen A;

Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); Kurt Schibler [[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)]; Luc Brion ([luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)); Martin Keszler ([mkeszler@wihri.org](mailto:mkeszler@wihri.org)); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu); Meena Garg ([mgarg@mednet.ucla.edu](mailto:mgarg@mednet.ucla.edu)); Nelin, Leif; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Polin, Richard; Robin Ohls ([rohls@salud.unm.edu](mailto:rohls@salud.unm.edu)); [ronnie\\_guillet@urmc.rochester.edu](mailto:ronnie_guillet@urmc.rochester.edu); Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [[bsood@med.wayne.edu](mailto:bsood@med.wayne.edu)]; Truog, William (MD); Uday Devaskar ([UDEVASKAR@MEDNET.UCLA.EDU](mailto:UDEVASKAR@MEDNET.UCLA.EDU)); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)

**Subject:** Reconciling SUPPORT, BOOST, AND COT: Do we have all the information needed to understand the results and how they should be applied?

As Wally thinks, it may be that the differences in RR and OR for death in the different studies and in different phases of the same study are due to the play of chance and that with current technology and methods of care, the 85-89% saturation range will result in a higher overall mortality than the 91-95% sat range. However, on careful rereading of SUPPORT, BOOST, and COT, the findings seem very difficult to reconcile and worthy of detailed discussion and review of the findings.

To summarize, with the original algorithm, mortality with the lower saturation goal was significantly increased in SUPPORT (RR = 1.27 [1.01-1.60]; n=1316, all with the original algorithm). In contrast, there was no evidence of increased death with use of allegedly the same algorithm in either the first phase of BOOST II (RR=0.90 [0.70-1.15]; n=1259) or in the first phase of COT (OR = 1.00 (0.63-1.59 [adjusted for center, as appropriate in SUPPORT; total n =549). With the results in SUPPORT being just barely significant, a meta-analysis of these results with the original algorithm would clearly not be significant. While this finding ultimately could be good news that might possibly be of use in defending ourselves against the Public Citizen law suit, the data become more confusing in comparing the findings for mortality before and after installing the revised algorithm.

In BOOST II, the substantially higher deaths in the low sat group relative to the higher sat group after the revised algorithm was introduced was highly significant (RR = 1.45 [1.15-1.84] n= 1182) and resulted in a highly significant treatment x algorithm interaction. There was also a higher death rate in COT with the lower saturation goal after the revised algorithm was introduced (OR = 1.23 [0.75-2.01]; n = 543); the OR is high enough to be clinically important if it is real. Despite the limited power to identify interactions, a meta-analysis of the data from both BOOST II and COT might well indicate an overall treatment by algorithm interaction, a finding that of course would mean that the effect of the saturation goal on mortality was influenced by whether the original or revised algorithm was used. This would be disturbing for multiple reasons, including the difficulty in trying to explain why a higher mortality would occur with the revised algorithm if the calculated changes in true oxygen saturation in BOOST AND cot are in fact correct.

Shouldn't these results should make us concerned about the possibility that more than what we understand changed between the first and revised algorithm? This concern prompts the following kind of questions about SUPPORT that that I don't recall were addressed previously (though perhaps at a Steering Committee I missed –if so, I apologize for raising any questions that have already been well addressed.)

1. Abhik, would you please provide to the Network investigators the distribution of values for the DISPLAYED oxygen saturation values for each group as shown on the monitors in SUPPORT?

We need to see if we all agree that SUPPORT had the same bimodal saturation distribution for group with fewer than expected values in the 87-89% range as clearly documented by BOOST II investigators in their Figure 1 NEJM 2013; 368, (pg. 2096)?

The saturation distributions would be derived from a very large number of observations in BOOST and in SUPPORT. If the same bimodal distribution is not present in BOOST and SUPPORT, we need to dig further order to better understand the differences between the studies and be convinced that the "original" algorithms were in fact identical. Ref COT, it is hard to discern (at least to my eyes) from the

data presented in the manuscript or appendix whether a bimodal distribution occurred in that study similar to that in BOOST; we might want to ask if the COT investigators can provide such curves from what they collected, particularly if our distributions differ from those in BOOST. As I understand it, the bimodal distribution is the expected result of the algorithm itself (the reason Massimo revised it in response to the findings in BOOST) rather than the way NICU staff used the oximeters to adjust FiO<sub>2</sub>, right? If so, the absence of a bimodal distribution in either COT or SUPPORT would prompt further worry that the "original" algorithm was not exactly the same in SUPPORT, COT, and BOOST II.

2. How can we be certain that the method used to calculate TRUE saturation curves (what we call the "actual" saturation values in the SUPPORT figure 3) are correct and the same as in BOOST and COT when the original algorithm was used? Is there a way independent of the company to determine this?

According to the BOOST investigators noted (as stated bottom of left hand column to top of right hand column on page 2097) that "Displayed oxygen-saturation values *gradually reverted to actual values* when the measured value was outside the range of 85 to 95%." [italics mine]. In SUPPORT (1<sup>st</sup> column of page 1962), we note oxygen saturation "...reverted to actual (nonskewed) values when it was less than 84% or higher than 96%.." ( The same is noted for COT.) Might the subtle difference in wording reflect a subtle but important difference (or perhaps even a sizable unintended difference) in the actual algorithm or the method to calculate the true saturation values?

3. In SUPPORT and COT, the oxygen saturations curves are display in terms of the median saturations for individual infants. Median values of course do not indicate the proportion of time that infants had extreme value. It is hard to compare the studies with respect to the proportion of time that infants spent at different saturation values in the different studies. This is important to understanding whether the mortality differences reflect differences in the % of time spent at very low (or possibly even very high) saturations. Abhik can you send (or if I missed it, please resend) figures for SUPPORT constructed like those in BOOST II Figure 1 showing percent of time spent at different saturations as a % of total time receiving oxygen.

4. Ref the generalizability of SUPPORT findings to current practice, has Massimo indicated that the values displayed on oximeters now in use are identical to what would the ones calculated as the "actual" value with both the original and revised algorithms in the different trials and hasn't been tinkered with again?

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**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Distribution of saturations  
**Date:** Wednesday, November 20, 2013 9:56:18 AM  
**Attachments:** Distribution of SUPPORT Oxygen Saturations 20130521.docx

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FYI, this is work done by Marie a while back that may be relevant. Talk to you soon.

Thanks

Abhik

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**From:** Gantz, Marie  
**Sent:** Tuesday, May 21, 2013 3:04 PM  
**To:** 'Finer, Neil'; Das, Abhik; Wally Carlo, M.D.; Rich, Wade  
**Subject:** RE: Distribution of saturations

Thanks, Neil. The explanation of why we have some infants with lower medians and COT does not makes sense. I added a table to the end of the attached version of the document to answer your question. Medians and means remain very similar to what they were before, but I have added ranges that match the ones in the COT tables.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-907-5110

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Saturday, May 18, 2013 3:54 AM  
**To:** Gantz, Marie; Das, Abhik; Wally Carlo, M.D.; Rich, Wade  
**Subject:** RE: Distribution of saturations

Many thanks Marie

I have always suspected that a major difference between SUPPORT and the other trials is the fact that we enroll infants by 2 hours

There are sick infants who never stabilize and we include them as you describe – whereas I suspect none of these will be enrolled in the other trials

Thus infants with medians < 80% will be more in our trial and will pull the median to the left

I assume that your previous values for median and mean % of times with SpO2 values < 80% remain OK

Can you send that Table again and include % < 85% as this is what COT reported

Thanks again

Neil

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]

**Sent:** Saturday, May 18, 2013 2:01 AM  
**To:** Finer, Neil; Das, Abhik; Wally Carlo, M.D.; Rich, Wade  
**Subject:** Distribution of saturations

Hi all,

Attached is a document describing the distributions of oxygen saturations in the SUPPORT oxygen target groups. Please let me know if you have any questions.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-507-5110

---

**From:** Gantz, Marie  
**Sent:** Wednesday, May 15, 2013 3:21 PM  
**To:** 'Finer, Neil'; Das, Abhik; 'Wally Carlo, M.D.'  
**Subject:** RE:

Thanks for the clarification.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-507-5110

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Wednesday, May 15, 2013 2:00 PM  
**To:** Gantz, Marie; Das, Abhik; Wally Carlo, M.D.  
**Subject:** RE:

Marie

The issue of death is NOT a suggestion for SUPPORT  
It is more a thought that may need to be looked at by COT!!!  
Neil

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**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Wednesday, May 15, 2013 6:52 PM  
**To:** Das, Abhik; Finer, Neil; Wally Carlo, M.D.  
**Subject:** RE:

To expand on the thought below, while I do think it makes sense to look to see if the curves look the same with the newer, improved version of the oximeter data, I think that additional exploration of

how the values relate to death should be done only in the context of a fully thought-out and approved analysis proposal. Abhik, do you agree?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-597-5110

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**From:** Das, Abhik  
**Sent:** Wednesday, May 15, 2013 12:50 PM  
**To:** Gantz, Marie; 'Finer, Neil'; 'Wally Carlo, M.D.'  
**Subject:** RE:

No, I agree that we need to check this out and understand the issues better.  
Thanks  
Abhik

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

**From:** Gantz, Marie  
**Sent:** Wednesday, May 15, 2013 12:46 PM Eastern Standard Time  
**To:** 'Finer, Neil'; Das, Abhik; Wally Carlo, M.D.  
**Subject:** RE:

Thanks, Neil. I think it makes sense to look again at the distribution of SpO2 values in the SUPPORT pulse oximetry groups. Note that the version of the oximetry data I have been working with recently differs from the version we used in November 2009 for the paper. When the paper was written I had not had a chance to do as much quality checking of the oximeter data, and we have since made a few adjustments including that James re-processed the data taking into account some protocol deviations where the infant was on the wrong oximeter (which impacts the transformation he does based on the oximeter skew), I have done some additional refinement in adjusting for the skew, and some additional data cleaning has been done such as excluding data for dates that don't make sense (like dates before the infant's DOB). So we might find that newer curves look a bit different, although I would not expect any major changes. I have been traveling for meetings the past two days, but I hope to look into this issue this week as long as Abhik does not have any objections.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-597-5110

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]

**Sent:** Wednesday, May 15, 2013 12:32 PM  
**To:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:**

Hi Abhik, Marie and Wally

I wanted to expand on my previous request to try to explain the differences between COT and SUPPORT and explain why I believe that this needs to be done

The COT Trial indicated in the discussion the following “

Smaller

proportions of infants had median saturations

below 85% or above 95% in

COT than in SUPPORT, whereas between

85% and 95% our distributions

of oxygen saturations in the 2 treatment

groups overlapped less than the

distributions of saturations in

SUPPORT (eFigure 2). These important

differences between the observed

saturation profiles in the 2 trials may

explain why we did not find excess

mortality in the low target group and

excess retinopathy in the high target

group.”

The accompanying editorial had the following comment

“In addition, although the saturation targets were the same

in the 3 studies, the actual saturation ranges these infants

were exposed to may have been different. COT achieved

tighter compliance with the targets and a wider separation

in saturation between the 2 groups than SUPPORT. Based

on the information available, it appears that the clinical staff

maintained SpO<sub>2</sub> at the target range and hence reduced the

exposure to extreme SpO<sub>2</sub> levels more effectively in COT than

in SUPPORT, which may also in part explain the different

results between these 2 trials.

Now we have Maries Tables which give the mean and median % of time at SpO<sub>2</sub> < 85%, <80% etc and the COT paper has this data in their published appendix

As you will note, SUPPORT infants spend less % of time ( Medians, which is what I assume COT is reporting, although even with Means the data looks very similar) < 80%

I have been racking my feeble mind to understand these results

Is it that COT had some babies with high percentages both Low and High but the medians were OK?

These babies would have been very labile – we need to know if this is the reason – and see whether such infants had more death etc.

In any case we need to know and the reply to these suggestions

I think we need you to look carefully and confirm that our results are correct and that our curves are correct and then try to explain these differences

Many thanks for giving this matter your attention

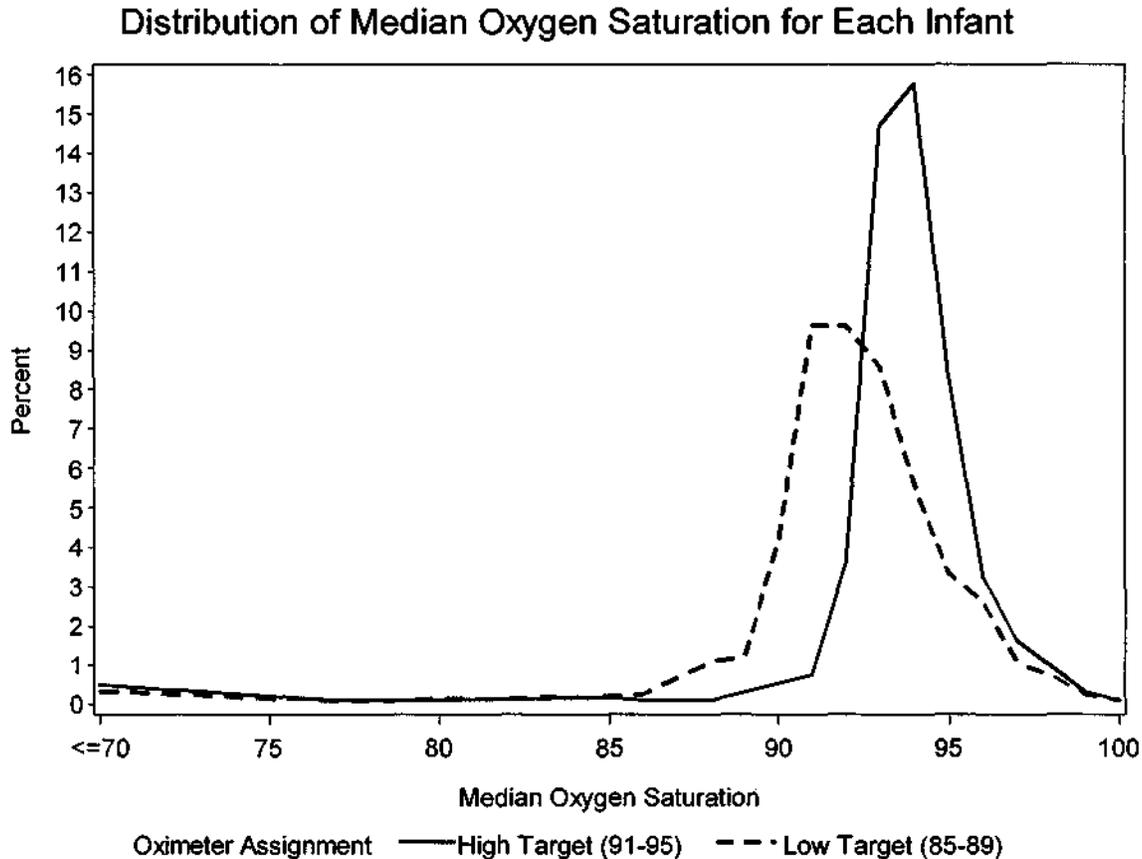
Neil

## Distribution of Actual Oxygen Saturations in the SUPPORT Low and High Target Groups

Marie Gantz 5/17/2013

Updated 5/21/2013: Legend of Figures 3a and 3b corrected, Table 2 added

In our 2010 NEJM manuscript, we included the following distribution of median oxygen saturations for infants assigned to the low and high target groups (Figure 1).

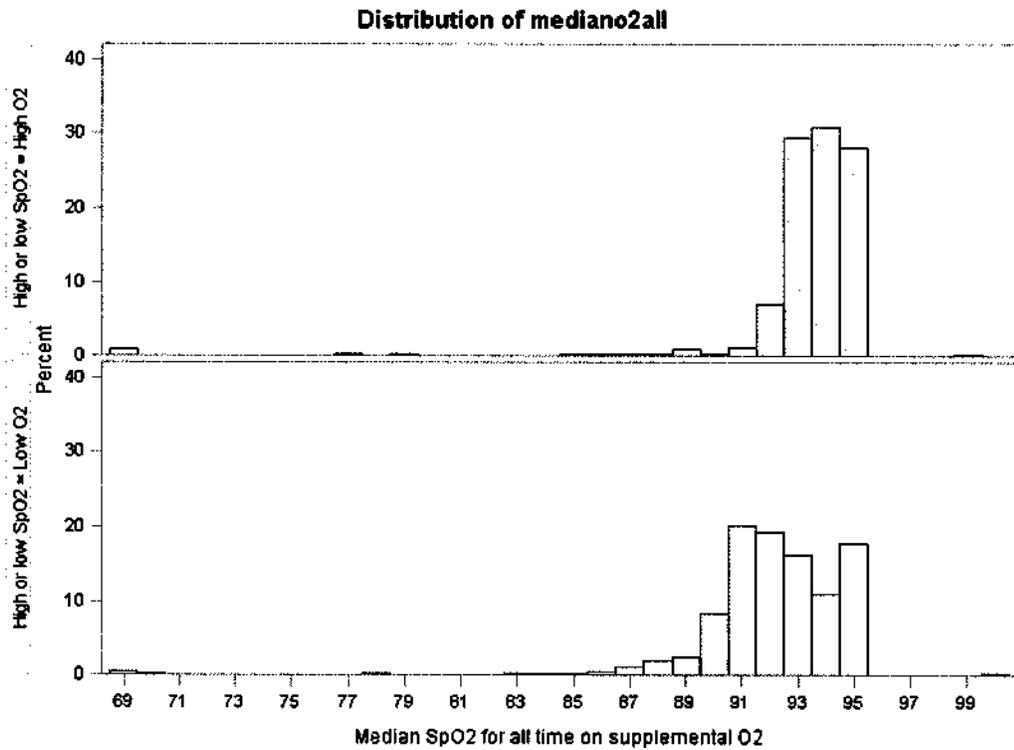


**Figure 1. Median oxygen saturations by infant from 2010 NEJM manuscript (percentages add to 100 over all infants)**

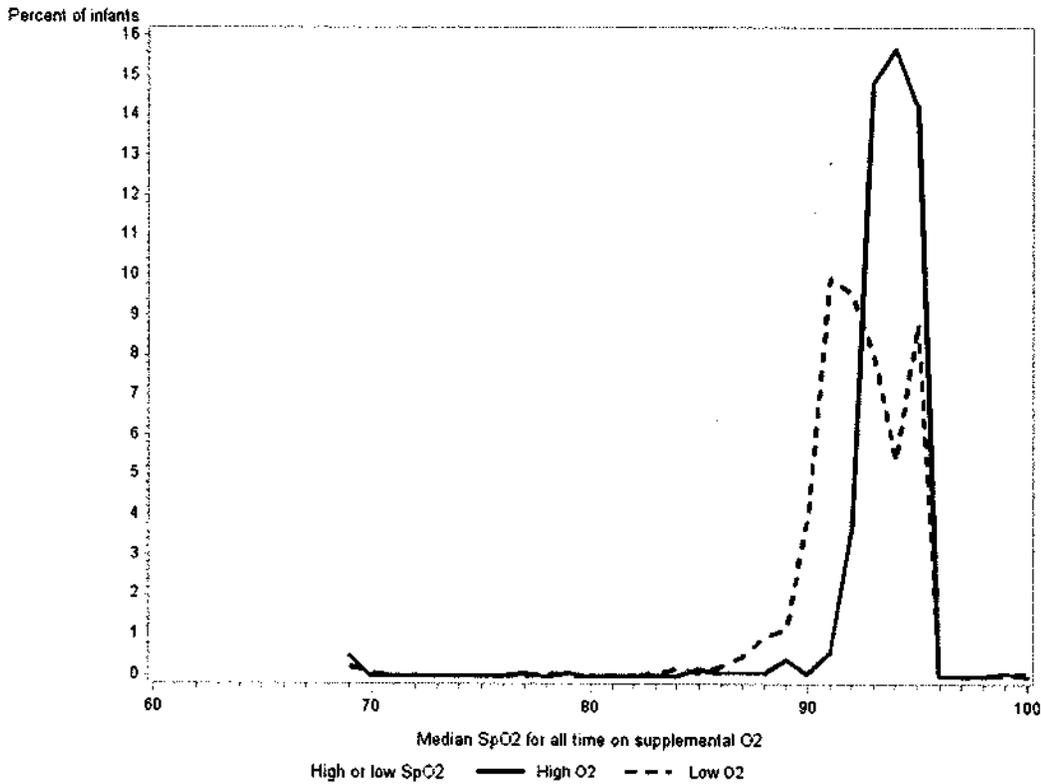
Since the November 2009 version of the oximeter data used for Figure 1, additional steps have been taken to refine the data including the following.

- Data from dates before the infants' DOB have been excluded.
- Oximeter data have been reprocessed, taking into account protocol deviations where infants were on the incorrect oximeter (which impacts the initial transformation from skewed to "actual" SpO<sub>2</sub> values base on the algorithm provided by Massimo).
- Minor adjustment made to the way oximeter data were matched to respiratory support data from forms SUPP05 and SUPP11, impacting the identification of time on oxygen.
- Smoothing of oximeter skew refined using quadratic and cubic interpolation.

Median oxygen saturation curves using the current version of the pulse oximeter data (March 14, 2013) are shown in Figures 2a and 2b (same data displayed two ways). Note that throughout the figures and tables, a value of 69 represents all oximeter values <70%.



**Figure 2a. Median oxygen saturations by infant from March 14, 2013 version of oximeter data (displayed as histogram, percentages add to 100 in each target group)**



**Figure 2b. Median oxygen saturations by infant from March 14, 2013 version of oximeter data (displayed as curves, percentages add to 100 over all infants)**

The main difference between the old and new figures is that most medians previously calculated to be above 95% are now estimated to be at 95%. This difference is likely due to the changes in the smoothing algorithm and/or to more accurate identification of time on oxygen (since we have observed that oxygen saturations for time on room air are more likely to be close to 100%). In Figure 1, the median of the infant-level median saturations was 92 in the low target group and 94 in the high target group. In Figures 2a and 2b, the medians are the same as in Figure 1. The full distributions of median oxygen saturations, by target group, are shown in Tables 1a and 1b.

As a side-note, the data presented from the COT trial look more like the Figure 1 SUPPORT data in that there are more medians above 95%. This could be due to the inexact identification of time on oxygen used in COT (due to limitations of their data collection, they are including all oximeter data from days with >12 hours of supplemental oxygen). Also, COT is using cubic smoothing of the oximeter data, while we are using primarily quadratic smoothing (because it seems to perform better). I do not expect difference in the smoothing algorithm to result in large differences in the curves, though. I expect that the inclusion of time on room air (likely with saturations near 100%) would have a bigger impact on the curves.

<b>Median SpO2 for all time on supplemental O2</b>				
<b>mediano2all</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
69	3	0.50	3	0.50
70	1	0.17	4	0.66
78	1	0.17	5	0.83
83	1	0.17	6	0.99
84	2	0.33	8	1.32
85	1	0.17	9	1.49
86	3	0.50	12	1.98
87	6	0.99	18	2.97
88	12	1.98	30	4.95
89	14	2.31	44	7.26
90	50	8.25	94	15.51
91	122	20.13	216	35.64
92	117	19.31	333	54.95
93	98	16.17	431	71.12
94	66	10.89	497	82.01
95	108	17.82	605	99.83
100	1	0.17	606	100.00

**Table 1a. Median oxygen saturations by infant: low target group (March 14, 2013 version of oximeter data)**

**Median SpO2 for all time on supplemental O2**

<b>mediano2all</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>69</b>	6	0.97	6	0.97
<b>77</b>	1	0.16	7	1.13
<b>79</b>	1	0.16	8	1.29
<b>85</b>	2	0.32	10	1.61
<b>86</b>	1	0.16	11	1.77
<b>87</b>	1	0.16	12	1.94
<b>88</b>	1	0.16	13	2.10
<b>89</b>	5	0.81	18	2.90
<b>90</b>	1	0.16	19	3.06
<b>91</b>	7	1.13	26	4.19
<b>92</b>	44	7.10	70	11.29
<b>93</b>	182	29.35	252	40.65
<b>94</b>	192	30.97	444	71.61
<b>95</b>	175	28.23	619	99.84
<b>99</b>	1	0.16	620	100.00

**Table 1b. Median oxygen saturations by infant: high target group (March 14, 2013 version of oximeter data)**

In the SUPPORT data, there are 13 infants (5 in the low target group and 8 in the high target group) with median oxygen saturations below 80%. All of these infants died within the first two days of life, and the number of hours of oximeter data for each infant is limited: median 6.8 hours, IQR 4.4-13.2 hours, range 0.6-41.2 hours. Similarly, the two cases with medians over 95% are based on limited data. One infant in the low target group had 2 hours of oximeter data from day of life 8 and a median oxygen saturation of 100%, and one infant in the high target group had 6 hours of data from day of life 5 and a median oxygen saturation of 99%.

Looking at the distribution of infant-level medians might not be the best way to judge how well infants were kept within their target ranges. As an alternative, Figures 3a and 3b summarize the infant-level distributions of all oxygen saturations during time on oxygen. The lines represent the median percent of time infants spent at each saturation value. The boxes represent the 25<sup>th</sup> to 75<sup>th</sup> percentiles, and the whiskers represent the 5<sup>th</sup> to 95<sup>th</sup> percentiles.

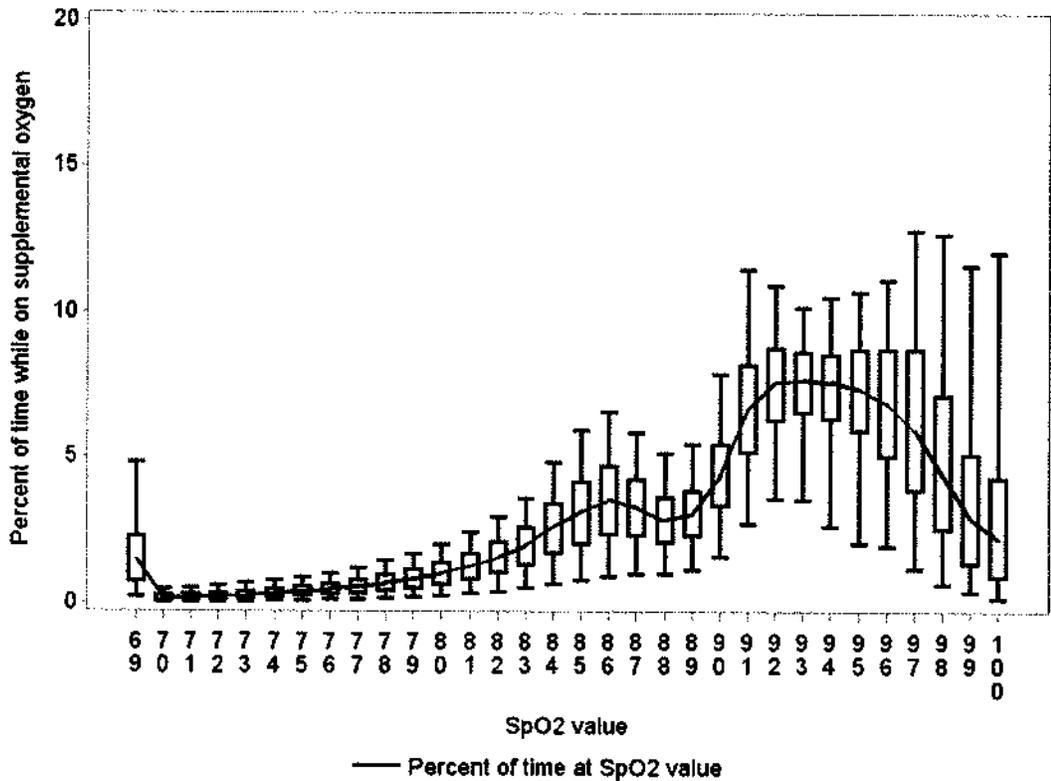


Figure 3a. Summary of infant-level distributions of oxygen saturations: low target group (March 14, 2013 version of oximeter data)

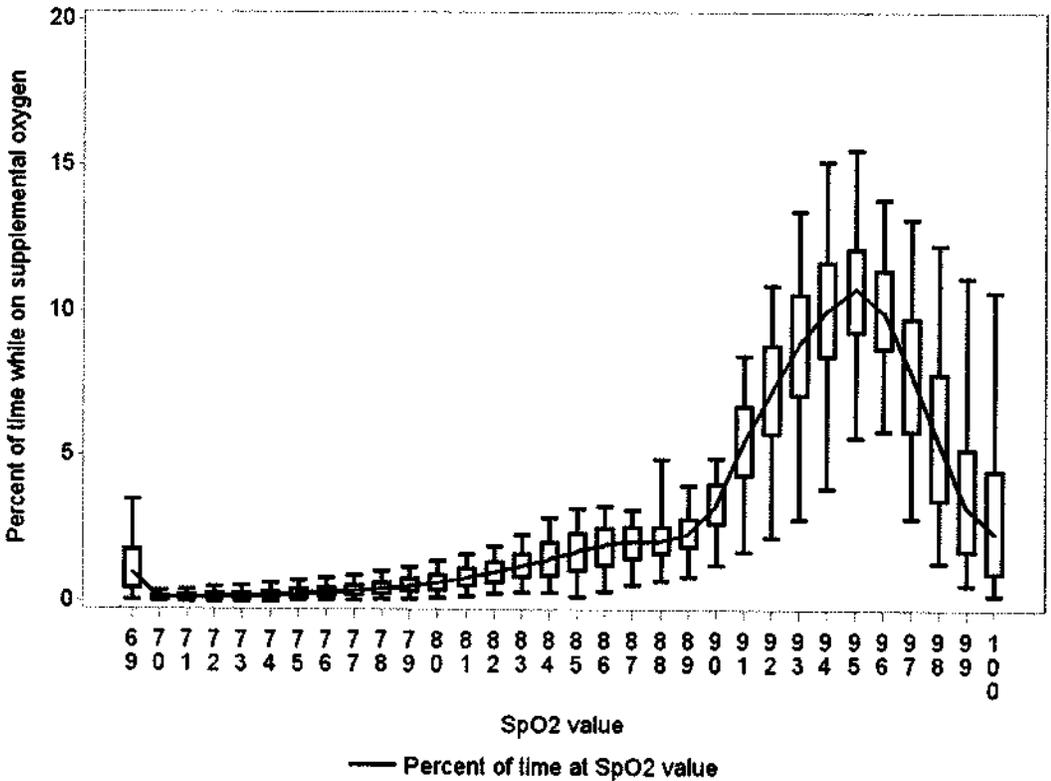


Figure 3b. Summary of infant-level distributions of oxygen saturations: high target group (March 14, 2013 version of oximeter data)

Table 2 shows the percent of time spent in various oxygen saturation ranges for infants assigned to the low and high target groups.

<b>Infant-Level Oxygen Saturations</b>	<b>Low Target Group</b>	<b>High Target Group</b>
Median saturation: median (IQR)	92% (91%, 94%)	94% (93%, 95%)
Time spent >98%: median (IQR)	5.2% (2.5%, 9.6%)	5.9% (2.9%, 10.2%)
Time spent >95%: median (IQR)	23.1% (14.9%, 34.8%)	30.6% (22.7%, 38.6%)
Time spent <85%: median (IQR)	15% (10.3%, 19.3%)	9.3% (6.1%, 12.8%)
Time spent <80%: median (IQR)	5.9% (3.9%, 8.6%)	4% (2.3%, 5.9%)
Time spent <70%: median (IQR)	1.5% (0.8%, 2.4%)	1% (0.5%, 1.8%)
Time spent >98%: mean (95% CI)	8% (7.2%, 8.7%)	8.4% (7.7%, 9.2%)
Time spent >95%: mean (95% CI)	26.7% (25.3%, 28%)	33% (31.7%, 34.2%)
Time spent <85%: mean (95% CI)	16% (15.2%, 16.8%)	10.9% (10.1%, 11.7%)
Time spent <80%: mean (95% CI)	7.3% (6.6%, 7.9%)	5.5% (4.7%, 6.2%)
Time spent <70%: mean (95% CI)	2.5% (1.9%, 3%)	2.1% (1.5%, 2.6%)

**Table 2. Percent of time spent in various oxygen saturation ranges while receiving supplemental oxygen for infants randomized to low and high target groups (March 14, 2013 version of oximeter data)**

**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale  
**Subject:** RE: SUPPORT slide  
**Date:** Sunday, November 17, 2013 8:26:05 PM

---

I don't see a problem with letting Abbott have it unless it would compromise publication. It will be in press very soon if I could get an answer about dealing with authors who fail to respond to multiple emails. Maybe we could send the data or the figures from the PAS poster that's already published.

Sent from my Windows Phone

**From:** Higgins, Rosemary (NIH/NICHD) [E]<<mailto:higginsr@mail.nih.gov>>  
**Sent:** 11/17/2013 6:39 PM  
**To:** Phelps, Dale<[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)>  
**Cc:** Kennedy, Kathleen A<<mailto:Kathleen.A.Kennedy@uth.tmc.edu>>  
**Subject:** Re: SUPPORT slide

Dale

This is not my decision - requires a steering committee vote. What is the time frame from Abbott nutrition?

Thanks

Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Nov 17, 2013, at 5:05 PM, "Phelps, Dale"

<[Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)<[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)>> wrote:

Hi Larry,

We have a similar slide (same dataset) that is in a manuscript that has just been accepted for publication.

The first author is Kathleen Kennedy and it is a NRN paper.

I will ask Dr. Higgins and Dr. Kennedy if we may be able to share with you that graph of the rates of survival, ROP and severe ROP from the SUPPORT trial data.

That will give you final and peer reviewed data.

If NICHD approves, you would be able to use it within a confidential internal setting until it gets published.

(maybe published on line early?)

Once published, you can of course use it freely.

Dale Phelps

**From:** Williams, Larry W [<mailto:Larry.Williams@abbott.com>]  
**Sent:** Monday, October 21, 2013 8:51 AM  
**To:** Phelps, Dale  
**Subject:** RE: SUPPORT slide

Thanks Dale, I understand reasons you might not be able to share. Just let me know.

Larry

**From:** Phelps, Dale [[mailto:Dale\\_Phelps@URMC.Rochester.edu](mailto:Dale_Phelps@URMC.Rochester.edu)]  
**Sent:** Monday, October 21, 2013 11:42 AM

To: Williams, Larry W; Rosemary Higgins (higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>)  
Subject: RE: SUPPORT slide

Hi Larry,

I do not think that slide is considered "published" (from a Poster at a research meeting), so I'll have to check with Dr. Kennedy (first author of paper) and Dr. Higgins before letting you use it. Also I should type up the 'conditions' around the SUPPORT trial so you would understand its limitations... i.e. that SUPPORT was in-borns only (no transports) and enrolled infants only of 24, 25, 26, and 27 weeks gestation.

Also: in that slide, "sROP or death" is not equal to "sROP or death before ROP outcome" (but it is close)

With those caveats, I think you could use it wisely.

Dale

From: Williams, Larry W [mailto:Larry.Williams@abbott.com]

Sent: Monday, October 21, 2013 8:18 AM

To: Phelps, Dale; Rosemary Higgins (higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>)

Subject: SUPPORT slide

Dale,

Are you able to share the single slide you showed last week of ROP and mortality (and other outcomes) vs. gestational age that came from SUPPORT data? That slide was a very nice summary of several issues pertinent to INS3. I want to be able to use it internally (only) at Abbott to educate on the importance of ROP in the preterm population.

I enjoyed chatting with you at the meeting. And as both Kelly and I indicated, clearly many of the coordinators are obviously superb at what they do.

Larry W. Williams MD  
Senior Medical Director  
Abbott Nutrition Scientific and Medical Affairs  
3300 Stelzer Road  
Columbus OH 43219

**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Truog, William  
**Subject:** FW: ROP Secondary Manuscript #13-551 Decision - please respond  
**Date:** Tuesday, November 12, 2013 9:57:57 AM  
**Attachments:** [Acknowledgments \(Supplement for ROP Natural History Study Manuscript\).docx](#)  
[Figure 1.pdf](#)  
[Figure 3.pdf](#)  
[Figure 4.pdf](#)  
[ROP Natural History Study Manuscript \(for submission to J Perinatol\).doc](#)  
[ROP Natural History Study Manuscript \(for resubmission to J Perinatol\).doc](#)  
[Figure 2 \(revised\).pdf](#)  
[J Perinatology Response Letter.doc](#)

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Rose, I had already heard from you. Sorry for the confusion. I still haven't received responses from Roger, Marie, or Wade. Last time it took an email from you, so I thought maybe copying you would help. I don't understand why this is so difficult. Am I going about it the wrong way? Am I the only one who cares if the authors have actually done what they're going to say they did?

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Kennedy, Kathleen A  
**Sent:** Monday, November 11, 2013 9:35 AM  
**To:** 'Roger.Faix@hsc.utah.edu'; 'Gantz, Marie'; 'wrich@ucsd.edu'  
**Cc:** Higgins, Rosemary (NIH/NICHD); Archer, Stephanie  
**Subject:** FW: ROP Secondary Manuscript #13-551 Decision - please respond

I'd really like to get this back to Journal of Perinatology tomorrow. Please send me your comments or approval **today**. Thanks.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

## Acknowledgments

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Betty R. Vohr, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN; Dan Gingras, RRT; Regina A. Gargus, MD FAAP; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MD CAES; Martha R. Leonard, BA BS; Sarah Lillie, RRT; Kalida Mehta; James R. Moore, MD; Lucy Noel; Suzy Ventura; Rachel V. Walden; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kimberly Yolton, PhD; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP;

Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Susan R. Hintz, MD MS Epi; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; Elisabeth C. McGowan, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nysten, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Yvonne E. Vaucher, MD MPH; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Michael J. Acarregui, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janell Fuller, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Gary David Markowitz, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augustino; Julie Babish Johnson, MSW; Erica Burnell, RN; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Jon E. Tyson, MD MPH; Patricia W. Evans, MD; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Anna Bodnar, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel

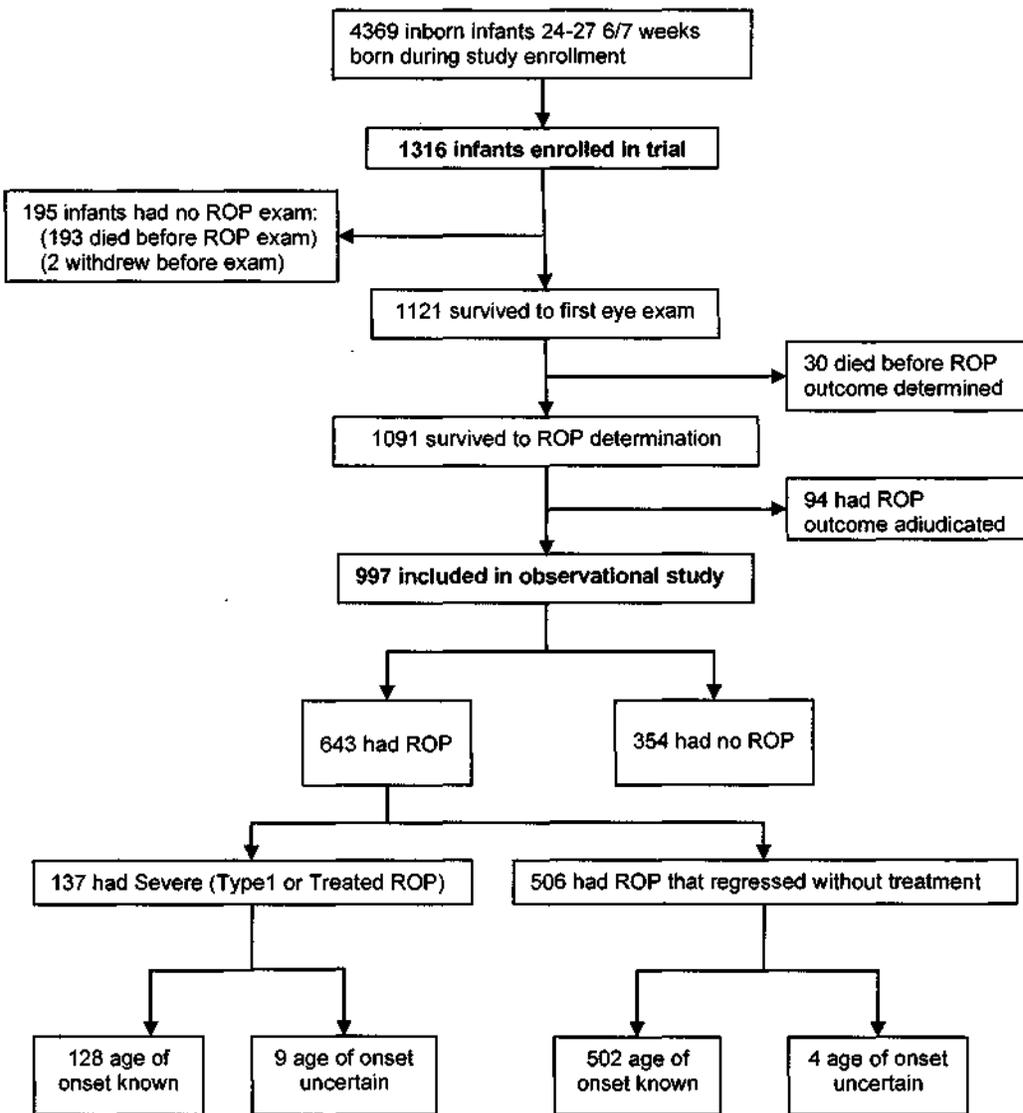
Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

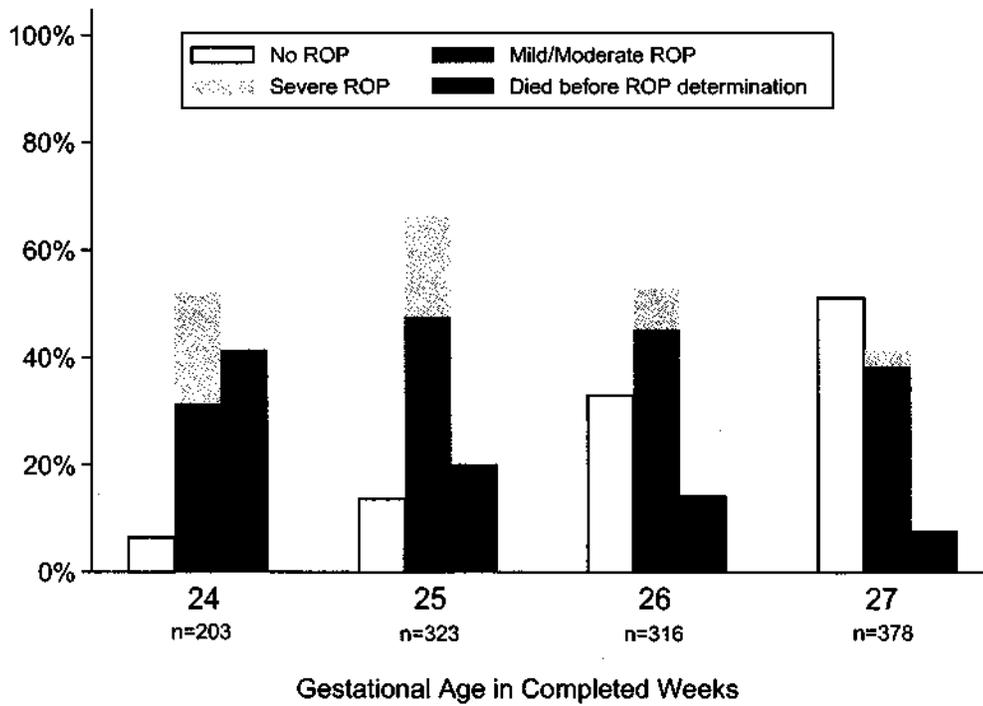
Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

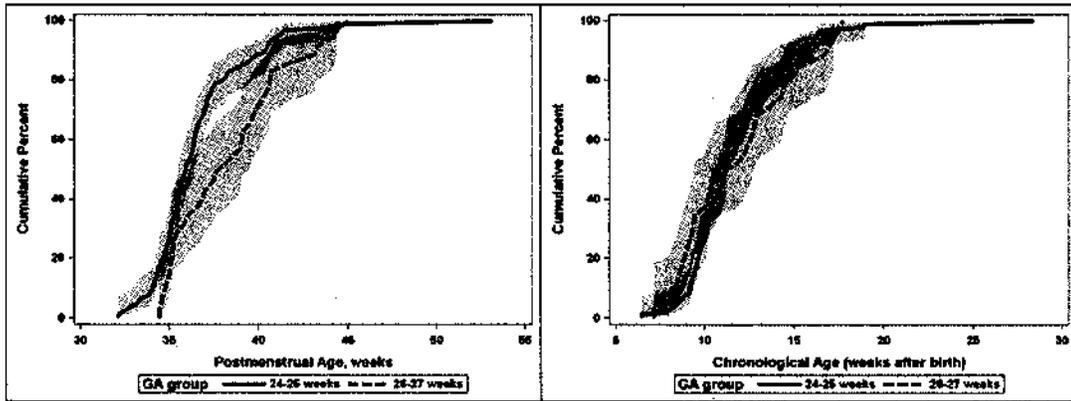
Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

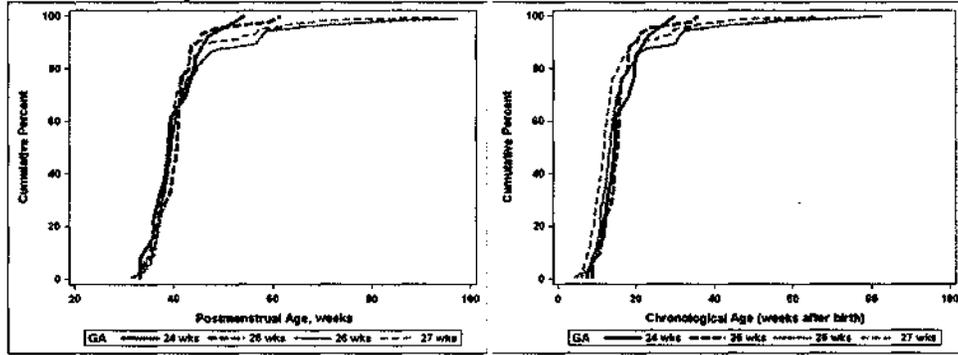
Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.



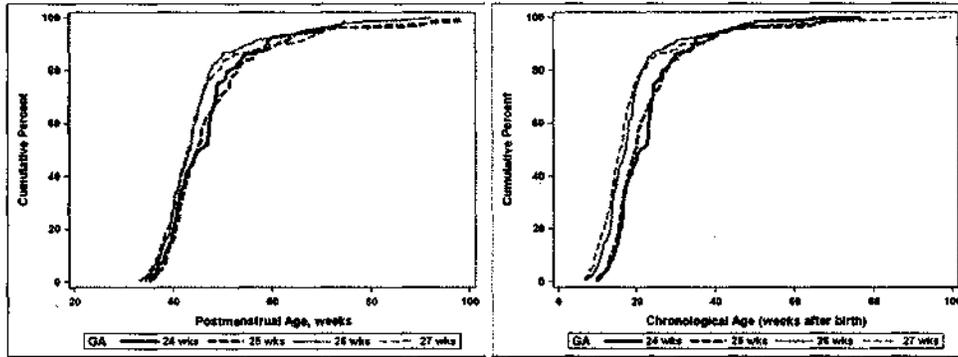




### No ROP on any exam



### Mild/Moderate ROP





**Medical School**  
Department of Pediatrics  
Division of Neonatal-Perinatal Medicine  
Center for Clinical Research and Evidence-Based Medicine

Kathleen A. Kennedy, MD, MPH  
*Richard W. Minkoff Professor of Pediatrics*  
Director, MS in Clinical Research Degree Program

October 10, 2013

Edward E. Lawson, MD  
Editor  
c/o Sue Ann Nelson  
75 Varick Street, 9<sup>th</sup> Floor  
New York, NY 10013

Dear Dr. Lawson:

The authors thank the reviewers for their careful review of the attached manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants". The following changes were made to address the reviewers' suggestions:

1. The reference for the 2013 screening guidelines was moved to the abstract as requested. Additional detail about the guidelines could not be added to the abstract without exceeding the word limit for the abstract. The criteria for beginning screening are delineated in the first paragraph of the Introduction.
2. The sentence in the conclusion has been qualified to apply to infants eligible for the SUPPORT trial.
3. The 137 infants with severe ROP was also given as a % of infants with ROP determination. The numerator and denominator are specified for the 1.4%.
4. Two references are cited for the AAP screening recommendations that were in place at the time of the study. The 2001 guidelines applied when the study began in 2005; the 2006 guidelines were released within a year after enrollment began.
5. This suggested sentence has been added to the Conclusion in the Abstract.
6. See #2 above.
7. We are uncertain what interval is being requested. In this study (done after the ET-ROP study) infants' eyes were treated when they developed Type 1 ROP so there was no interval to measure between Type 1 and CRYO threshold ROP.
8. Type 1 ROP is defined in the second paragraph of the Introduction.
9. Details about the ROP exams are in the first paragraph of the Methods.
10. The drug category for bevacizumab has been specified in the first paragraph of the Methods. The types of ROP interventions that were included as treatment are also detailed in the first sentence of this paragraph. This sentence is referenced later in the paragraph (second-to-last sentence) where the term "surgery" is used. This sentence also states that severe ROP was defined when the criteria were met in either eye.
11. "Gestational Age" has been added to the x-axis for the Figure 2.
12. The "Any ROP" column has been added to Table 2.



**Medical School**  
Department of Pediatrics  
Division of Neonatal-Perinatal Medicine  
Center for Clinical Research and Evidence-Based Medicine

Kathleen A. Kennedy, MD, MPH  
*Richard W. Mithoff Professor of Pediatrics*  
*Director, MS in Clinical Research Degree Program*

13. A "Cumulative Percent" row title has been added to Table 3. Another sentence has been added to the fourth paragraph of the Results to highlight the important findings in Table 3. We have used the terms postmenstrual age and chronological age as recommended by the AAP (Engle WA et al. Age terminology during the perinatal period. Pediatrics 114: 1362-1364, 2004.)
14. The shaded areas have been designated in the legend for Figure 3.
15. The numbers in the last row of Table 4 have been removed and the differences between the two groups have been highlighted in the text (last paragraph in Results). *(may need to change this if decide to try to include numbers for severe ROP after discharge in infants who were back transferred)*
16. The description of the data in Table 5 in the text has been expanded and expressed differently in the last paragraph of the Results to highlight ROP exam findings that put infants at the highest risk for severe ROP after discharge.
17. It isn't entirely clear what "magnitude estimate" is requested. We restated the percent of infants who were diagnosed with severe ROP after discharge in the fifth paragraph of the Discussion.
18. The required use of the International Classification of ROP has been added to the Methods. The lack of certification for examiners has now been added to the paragraph about limitations.

The Acknowledgments section has been moved to a Supplement as requested. There is a conflict of interest statement in the manuscript.

These changes have undoubtedly improve the clarity of the manuscript. We again thank the reviewers and editors for their suggestions and consideration.

Sincerely,

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## **Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

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### **Running title:** Retinopathy of Prematurity Screening Criteria

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## **Abstract**

**Objective:** To determine if current retinopathy of prematurity screening guidelines<sup>1</sup> adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

**Study Design:** Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics (AAP) screening recommendations, beginning by 31-33 weeks postmenstrual age.<sup>2,3</sup>

**Results:** 1316 infants were enrolled in the trial. 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 (14% of 997) met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data (without missing or delayed exams) to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% (14/997) developed severe retinopathy of prematurity after discharge.

**Conclusion:** Our contemporary data support the 2013 AAP screening guidelines for ROP for infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age.<sup>1</sup> Some infants do not meet treatment criteria until after discharge home. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

**Keywords (not in title):** extremely premature infant

## **Introduction**

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,4</sup> are based on natural history data from the CRYO-ROP<sup>5</sup> and LIGHT-ROP<sup>6</sup> studies. The CRYO-ROP study<sup>7</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.<sup>8</sup> Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.<sup>9,10</sup> For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>9</sup> The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.<sup>5</sup> It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) / American Academy of Ophthalmology (AAO) / American Association of Pediatric Ophthalmology and Strabismus (AAPOS) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.<sup>1</sup> The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>6</sup> Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II.<sup>11</sup> Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening

criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely identification of Type 1 ROP. There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial<sup>12</sup> and a population-based cohort study of infants born 2004-2007 in Sweden<sup>13</sup> reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants  $\leq 27$  weeks gestation;<sup>14</sup> this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort<sup>15</sup> reported that “No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively”; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 <sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>16</sup> to determine

**if the current ROP screening guidelines are still appropriate for timely identification of Type 1 ROP in a contemporary cohort of infants.**

## Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP [defined as Type 1 ROP or treatment with laser ablation, cryotherapy, bevacizumab (monoclonal antibody to vascular endothelial growth factor) injection, scleral buckle, or vitrectomy] or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.<sup>16</sup> Inborn infants 24<sup>0/7</sup>–27<sup>6/7</sup> weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Study eye examinations were performed by each site's examining ophthalmologists using the International Classification of ROP.<sup>17</sup> Ophthalmology exams began no later than 31–33 weeks postmenstrual age, as recommended in the AAP/AAO/AAPOS guidelines that were in place when the study began.<sup>2,3</sup> Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center, based on the findings of the previous examination. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP first treated with peripheral retinal ablation, vitreoretinal surgery or bevacizumab injection as detailed above) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, “age of onset” was defined as the postmenstrual or chronological age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time interval prior to detection. Infants with Type 1 ROP whose first exam with Type 1 ROP was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule (adjudicated ROP outcomes) were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for continuous data grouped into quantiles.<sup>18</sup> Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

## **Results**

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among

infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to “onset” exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without various ROP categories are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.<sup>19,20,21</sup> Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ( $p < 0.05$  for all comparisons of no ROP vs any ROP).

For infants who had any stage of ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. Of note, 6.4 weeks was the minimum (youngest) chronologic age at which severe ROP was seen; 95% of cases had occurred by 17 weeks chronologic age. Also, 25% of severe ROP was identified after 38.6 weeks postmenstrual age and 5% was identified after 43.3 weeks. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (lower oxygen saturation and higher oxygen saturation target ranges) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to

prior studies,<sup>5</sup> our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ( $p < 0.01$ ). There is no significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ( $p < .0001$ ).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge home are shown in Table 4. Infants with severe ROP identified after discharge had onset of ROP at a later postmenstrual age and were discharged at an earlier postmenstrual age than infants who had severe ROP identified before discharge. In this referral center cohort of 997 infants, 1 infant (0.1%; or 0.7% of 137 infants with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4% of the cohort; or 10% of infants with severe ROP) reached severe ROP after discharge home. Among the 14 infants with severe ROP identified after discharge home, 4 had been transferred to lower

acuity neonatal intensive care units prior to discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the last pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While infants with vessels in Zone I or with ROP in Zone II on the last pre-discharge exam were at the highest risk for developing severe ROP after discharge (1/4=25% and 10/206=5%, respectively), 1 case of severe ROP after discharge (1/82=1%) occurred in an infant with ROP in Zone III on the last exam before discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but we did not identify any clinical risk factors in our data that clearly identify infants at risk to develop severe ROP after discharge.

## Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2003,<sup>11</sup> so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies<sup>5</sup> in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,<sup>5</sup> lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP/AAO/AAPOS that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,<sup>1</sup> albeit with a caution that the data

supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$  g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>22</sup> Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>23</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,<sup>13</sup> which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al<sup>14</sup> included 23-27 week infants; infants  $\leq 25$  weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants  $>25$  weeks. In this study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian study,<sup>14</sup> the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al<sup>15</sup> that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged ~~or transported to a lower acuity neonatal unit closer~~ to home. We have not identified any other studies that report the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study (1.4% of the cohort and 14% of the infants with severe ROP), the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up after discharge. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who did not develop Type 1 ROP after discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>24</sup> The SUPPORT trial inclusion criteria limit the generalizability of these data to

infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 <sup>6</sup>/<sub>7</sub> weeks. The ophthalmology exams for this study were performed by each unit's examining ophthalmologists according to AAP/AAO/AAPOS recommendations using the international classification of ROP but with no formal certification for the study. This might lead to more inconsistency or random error than would occur under strict study exam protocols, but it more closely reflects what typically occurs in clinical practice.

Current AAP/AAO/AAPOS screening guidelines, published in 2013,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (0.7% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge home. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such

rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>24</sup>

**Conflict of Interest:** The authors declare that they have no financial interests related to the work described in this manuscript.

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**Figure Legends:**

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome (997 survivors + 223 infants who died)

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals (shaded areas)

Figure 4. Postmenstrual and chronological age of “favorable outcome” (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP <sup>1</sup> Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/Moderate ROP	Severe (Type I or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD <sup>2</sup> )]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age <sup>3</sup> [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Standard deviation

<sup>3</sup> Based on Olsen<sup>25</sup> growth curves

Table 2. Risk factors for ROP<sup>1</sup>

Risk Factor	No ROP <sup>2</sup>	Any ROP (Mild, Moderate, or Severe)	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	354	643	506	137
Days on supplemental oxygen <sup>3</sup> [median (IQR <sup>4</sup> )]	33 (10, 60)	66 (39, 100)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [(n (%))]	75 (21)	247 (38)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	23 <sup>5</sup> (4)	15 <sup>5</sup> (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	98 <sup>5</sup> (15)	69 <sup>5</sup> (14)	29 (21)
Proven necrotizing enterocolitis <sup>6</sup> [n (%)]	20 (6)	72 (11)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	365 (57)	271 (54)	94 (69)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> p<0.05 for all comparisons of No ROP vs Any ROP (mild, moderate, or severe)

<sup>3</sup> Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days

<sup>4</sup> Interquartile range

<sup>5</sup> Missing data for 1 infant

<sup>6</sup> Modified Bell's stage II or III<sup>26</sup>

Table 3. Postmenstrual and chronological age of onset<sup>1</sup> [with 95% confidence intervals (CI<sup>2</sup>)] of any stage ROP<sup>3</sup> (among infants with ROP age of onset determined)

		Cumulative Percent with Onset of ROP (by age of onset and ROP category)								
ROP type	n	Min <sup>4</sup>	1%	5%	25%	50%	75%	95%	99%	Max <sup>4</sup>
Postmenstrual Age (weeks)										
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP <sup>5</sup> (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Cumulative Percent with Onset of ROP (by age of onset and ROP category)								
ROP type	n	Min	1%	5%	25%	50%	75%	95%	99%	Max
Chronological Age (weeks)										
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP <sup>3</sup> (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For “Any ROP”, this is the first exam with any stage of ROP in any zone.

<sup>2</sup> Confidence interval

<sup>3</sup> Retinopathy of prematurity

<sup>4</sup> Min = minimum age at which designated severity of ROP was identified; max = maximum age.

<sup>5</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

**Table 4. Postmenstrual age of severe ROP<sup>1</sup> onset and discharge for infants with severe ROP determined before and after discharge home**

Infants with Severe ROP N=137	First exam with severe ROP occurred <u>before</u> discharge to home n=123	First exam with severe ROP criteria occurred <u>after</u> discharge to home <sup>2</sup> n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Among these 14 infants, 4 had been transferred back to lower acuity neonatal intensive care units prior to discharge home.

Table 5. ROP<sup>1</sup> exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

<sup>1</sup> Retinopathy of prematurity

Table 6. Risk factors for ROP<sup>1</sup> for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA <sup>2</sup> at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Gestational age

## **Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

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## **Abstract**

**Objective:** To determine if current retinopathy of prematurity screening guidelines adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

**Study Design:** Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics screening recommendations.

**Results:** 1316 infants were enrolled in the trial. 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data (without missing or delayed exams) to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% developed severe retinopathy of prematurity after discharge.

**Conclusion:** Our contemporary data support the 2013 screening guidelines. Some infants do not meet treatment criteria until after discharge home.

**Keywords (not in title):** extremely premature infant

## Introduction

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1, 2</sup> are based on natural history data from the CRYO-ROP<sup>3</sup> and LIGHT-ROP<sup>4</sup> studies. The CRYO-ROP study<sup>5</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.<sup>6</sup> Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.<sup>7,8</sup> For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>7</sup> The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.<sup>3</sup> It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.<sup>1</sup> The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed “CRYO-ROP threshold”). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>4</sup> Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II. Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely

identification of Type 1 ROP.<sup>9</sup> There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial<sup>10</sup> and a population-based cohort study of infants born 2004-2007 in Sweden<sup>11</sup> reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants  $\leq 27$  weeks gestation;<sup>12</sup> this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort<sup>13</sup> reported that “No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively”; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27 <sup>6</sup>/<sub>7</sub> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>14</sup> to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

## Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, bevacizumab, scleral buckle, or vitrectomy) or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.<sup>14</sup> Inborn infants 24<sup>0</sup>/<sub>7</sub>–27<sup>6</sup>/<sub>7</sub> weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Ophthalmology exams began no later than 31-33 weeks postmenstrual age, as recommended in the AAP guidelines in place when the study began.<sup>15,16</sup> Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this observational study, "age of onset" was defined as the postmenstrual or chronological age at which ROP or ROP of a given severity was detected, with the recognition that onset was some

time prior to detection. Infants with Type 1 ROP whose first exam with Type 1 ROP was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule (adjudicated ROP outcomes) were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for continuous data grouped into quantiles.<sup>17</sup> Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

## **Results**

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to “onset” exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-

Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.<sup>18,19,20</sup> Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ( $p < 0.05$  for all comparisons of no ROP vs any ROP).

For infants who had ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (lower oxygen saturation and higher oxygen saturation target ranges) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,<sup>3</sup> our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ( $p < 0.01$ ). There is no significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had

mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ( $p < .0001$ ).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. In this referral center cohort of 997 infants, 1 infant (0.1%; 0.7% of those with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4%; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the worst pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among infants whose exams had not reached final favorable status at the time of discharge). While a high proportion (71%) of the infants who developed severe ROP after discharge had ROP in Zone II prior to discharge, this is not a particularly discriminating finding since most (95%) of the infants with this finding did not develop severe ROP after discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but we did not identify any no risk factors in our data that clearly identify infants at risk to develop severe ROP after discharge.

## Discussion

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,<sup>9</sup> so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies<sup>3</sup> in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,<sup>3</sup> lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,<sup>1</sup> albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$  g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>21</sup> Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>22</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to

chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,<sup>11</sup> which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al<sup>12</sup> included 23-27 week infants; infants  $\leq 25$  weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants  $>25$  weeks. In this Canadian Network study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are consistent with the other recent studies. In the Canadian Network study,<sup>12</sup> the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al<sup>13</sup> that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged

or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study, the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>23</sup> The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants >27 weeks.

Current AAP screening guidelines, published in 2013,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (1% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>23</sup>

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**Figure Legends:**

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome (997 survivors + 223 infants who died)

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals

Figure 4. Postmenstrual and chronological age of “favorable outcome” (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

**Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study**

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP <sup>1</sup> Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/Moderate ROP	Severe (Type I or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD <sup>2</sup> )]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age <sup>3</sup> [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Standard deviation

<sup>3</sup> Based on Olsen<sup>24</sup> growth curves

Table 2. Risk factors for ROP<sup>1</sup>

Risk Factor	No ROP <sup>2</sup>	Mild/Moderate ROP	Severe (Treated or Type 1) ROP
n	354	506	137
Days on supplemental oxygen <sup>3</sup> [median (IQR <sup>4</sup> )]	33 (10, 60)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [n (%)]	75 (21)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	15 <sup>5</sup> (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	69 <sup>5</sup> (14)	29 (21)
Proven necrotizing enterocolitis <sup>6</sup> [n (%)]	20 (6)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	271 (54)	94 (69)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> p<0.05 for all comparisons of No ROP vs Any ROP (mild, moderate, or severe)

<sup>3</sup> Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days

<sup>4</sup> Interquartile range

<sup>5</sup> Missing data for 1 infant

<sup>6</sup> Modified Bell's stage II or III<sup>25</sup>

Table 3. Postmenstrual and chronological age of onset<sup>1</sup> [with 95% confidence intervals (CI<sup>2</sup>)] of any stage ROP<sup>3</sup> (among infants with ROP age of onset determined)

ROP type	n	Postmenstrual Age (weeks)								
		Min <sup>4</sup>	1%	5%	25%	50%	75%	95%	99%	Max <sup>4</sup>
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP <sup>5</sup> (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

ROP type	n	Chronological Age (weeks)								
		Min	1%	5%	25%	50%	75%	95%	99%	Max
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP <sup>3</sup> (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

(95% CI)										
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<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For "Any ROP", this is the first exam with any stage of ROP in any zone.

<sup>2</sup> Confidence interval

<sup>3</sup> Retinopathy of prematurity

<sup>4</sup> Min = minimum age at which designated severity of ROP was identified; max = maximum age.

<sup>5</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Timing of first exam meeting severe ROP<sup>1</sup> criteria in relation to discharge and transfer

Infants with Severe ROP N=137	First exam with severe ROP occurred <u>before</u> discharge to home n=123	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

<sup>1</sup> Retinopathy of prematurity

Table 5. ROP<sup>1</sup> exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

<sup>1</sup> Retinopathy of prematurity

Table 6. Risk factors for ROP<sup>1</sup> for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA <sup>2</sup> at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Gestational age

**From:** [Laughon, Matthew M](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Michael Cotten, M.D. \(michael.cotten@duke.edu\)](#); [Ronald Goldberg, M.D. \(ronald.goldberg@duke.edu\)](#)  
**Subject:** FW: Research Ethics Grand Rounds on 11/21  
**Date:** Thursday, November 07, 2013 2:00:33 PM

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Hi Rose,

Dan Nelson is the Director of our IRB and he asked me to present the clinicians and researchers side of the story of SUPPORT. As you know, UNC did not enroll any participants as we started on Jan 1, 2009 enrolling in the GDB. I was going to use some of Jon Tyson's slides that he sent around but I really don't have that much time (15 minutes) to go over the whole study; I am going to focus on all the things that we do in the NICU that vary from site to site/clinician to clinician/etc. and how SUPPORT was within the recommended ranges of O2 sats (at the time).

FYI Nancy King is an attorney, use to work at UNC and is now at Wake Forest; she wrote a rebuttal on the OHRP/NIH website.

Let me know if you have questions.

Matt

**From:** Nelson, Daniel K  
**Sent:** Tuesday, October 22, 2013 6:19 PM  
**To:** [nmpking@wfubmc.edu](mailto:nmpking@wfubmc.edu); Laughon, Matthew M  
**Subject:** Research Ethics Grand Rounds on 11/21

Nancy and Matt,

Greetings to you both, and thanks for agreeing to participate in our grand rounds discussion on the SUPPORT trial. We are now one month away, so thought I would share some ideas in advance so you can be planning ahead and preparing.

I will be serving as session moderator, but certainly see the two of you as having the majority of the time. Matt will be speaking from the perspective of clinicians and scientists who conducted/supported the study, and Nancy will be representing those who have been critical of the study, as it was designed and conducted. Beyond or within those broad strokes, we have lots of flexibility. While the idea is to stake out both (all) sides of the argument, we don't need to approach as a classical "debate" with all of its trappings. On that background, here is what I would propose as format:

- **(5 min) DAN introduces the controversy, with perhaps one slide showing timeline (study, accusations, dueling commentaries, lawsuits, public hearing, etc) and one slide highlighting the types of questions that have been raised (How should standard of care be studied? Was consent deficient? How could 23 IRBs be wrong? Should feds swoop in after the fact? etc).... Without attempting to answer. That's your job!**
- **(15 min) MATT lays out the need for study, results, defends study design, whatever**

- **(15 min) NANCY lays out the criticisms**
- **(5 min) MATT rebuttal**
- **(5 min) NANCY rebuttal**
- **(15 min) open discussion with you and audience**

AS AN ALTERNATIVE, if you would prefer to use up your entire time in one segment, rather than have two turns each, that would also be fine. The above was predicated on the assumption that each of you might raise something in your opening salvo to which the other might like to respond..... but we don't have to do it that way, if you would prefer to just have 20 min uninterrupted time to make your points.

Thoughts?? Dan

---

Daniel K. Nelson, Director  
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Adjunct Professor of Pediatrics  
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**From:** Shankaran, Seetha  
**To:** Tyson, Jon E  
**Cc:** richard.ehrenkrantz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade Rich; mgantz@rti.org; "Duara, Shahnaz" (SDuara@med.miami.edu); ofliner@ucsd.edu; moshea@wfubmc.edu; Phelos, Dale; Larola, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@lupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; Higgins, Rosemary (NRH/NICHD) [E]; cotted10@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward.bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@lupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_quillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Sood, Beena; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); Pappas, Athina; (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Yohr (byohr@wihri.org); (h) (6) @aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira.adams-chapman; Isabel Purdy (jpurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yofon; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Jones, Patrick M; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colajzy (tarah.colajzy@uiowa.edu); Yvonne Vaucher; (Deanna\_Maffett@urmc.rochester.edu); (kwynn@upa.chop.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Bara, Rebecca; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gaudin, Cheri; McDavid, Georgia E; Holly Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)  
**Subject:** Re: Slides addressing support  
**Date:** Thursday, November 07, 2013 12:52:39 PM

---

Thanks Jon  
Excellent slides  
Seetha

Sent from my iPhone

On Nov 7, 2013, at 10:41 AM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:

If you are asked to discuss/present/defend SUPPORT, some of the slides in the last part of this talk given at Emory last week may save you some trouble preparing slides. Some of you might also be interested in some of the thoughts presented ref standards for comparative effectiveness research.

<CER Emory for NRN.pptx>

**From:** Tyson, Jon E  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Slides addressing support  
**Date:** Thursday, November 07, 2013 11:05:46 AM

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Unfortunately, I fear this story is no where close to over.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, November 07, 2013 9:48 AM  
**To:** Tyson, Jon E  
**Subject:** RE: Slides addressing support

Thanks for sharing and persevering!

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, November 07, 2013 10:39 AM  
**To:** [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); Wade RIch; [mgantz@rti.org](mailto:mgantz@rti.org); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); 'Phelps, Dale'; Laroia, Nirupama; ([Vivek.Narendran@cchmc.org](mailto:Vivek.Narendran@cchmc.org)); Anthony Piazza ([Anthony.Piazza@oz.ped.emory.edu](mailto:Anthony.Piazza@oz.ped.emory.edu)); Frantz, Ivan; ([suhas.kallapur@cchmc.org](mailto:suhas.kallapur@cchmc.org)); Abbot Laptook ([alaptook@wihri.org](mailto:alaptook@wihri.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org)); Ambal ([ambal@uab.edu](mailto:ambal@uab.edu)); Anna Maria Hibbs ([AnnaMaria.hibbs@cwru.edu](mailto:AnnaMaria.hibbs@cwru.edu)); [barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu); [bpindex@iupui.edu](mailto:bpindex@iupui.edu); [carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu); Carlton, David P; Higgins, Rosemary (NIH/NICHD) [E]; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [dstevenson@stanford.edu](mailto:dstevenson@stanford.edu); [dwallace@rti.org](mailto:dwallace@rti.org); Ed Bell ([edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Greg Sokol ([gsokol@iupui.edu](mailto:gsokol@iupui.edu)); Haresh Kirpalani ([KIRPALANI@email.chop.edu](mailto:KIRPALANI@email.chop.edu)); John Barks; Kennedy, Kathleen A; Krisa Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Kristi Watterberg ([kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)); Kurt Schibler ([kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)); Luc Brion ([luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)); Martin Keszler ([mkeszler@wihri.org](mailto:mkeszler@wihri.org)); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu); Meena Garg ([mgarg@mednet.ucla.edu](mailto:mgarg@mednet.ucla.edu)); Nelin, Leif; [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); Polin, Richard; Robin Ohls ([rohls@salud.unm.edu](mailto:rohls@salud.unm.edu)); [ronnie\\_guillet@urmc.rochester.edu](mailto:ronnie_guillet@urmc.rochester.edu); Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena ([bsood@med.wayne.edu](mailto:bsood@med.wayne.edu)); Truog, William (MD); Uday Devaskar ([UDEVASKAR@MEDNET.UCLA.EDU](mailto:UDEVASKAR@MEDNET.UCLA.EDU)); Wally Carlo ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)); ([apappas@med.wayne.edu](mailto:apappas@med.wayne.edu)); ([EMcGowan@tufts-nemc.org](mailto:EMcGowan@tufts-nemc.org)); Allison Payne; Andrea Duncan ([AFDuncan@salud.unm.edu](mailto:AFDuncan@salud.unm.edu)); Betty Vohr ([bvohr@wihri.org](mailto:bvohr@wihri.org)) (b)(6) [redacted]@aol.com; Gary Myers ([gary\\_myers@URMC.Rochester.edu](mailto:gary_myers@URMC.Rochester.edu)); [gold005@mc.duke.edu](mailto:gold005@mc.duke.edu); Hallam Hurt ([hurt@email.chop.edu](mailto:hurt@email.chop.edu)); Howard Kilbride ([hkilbride@cmh.edu](mailto:hkilbride@cmh.edu)); ira adams-chapman; Isabell Purdy ([ipurdy@mednet.ucla.edu](mailto:ipurdy@mednet.ucla.edu)); JaFuller@salud.unm.edu ([JaFuller@salud.unm.edu](mailto:JaFuller@salud.unm.edu)); Jean Steichen ([steichj@uc.edu](mailto:steichj@uc.edu)); Keith Yeates ([Keith.Yeates@nationwidechildrens.org](mailto:Keith.Yeates@nationwidechildrens.org)); Kim Yolton; Marsha Gerdes ([gerdes@email.chop.edu](mailto:gerdes@email.chop.edu)); Martha Colson; Myriam Peralta-Carcelen ([MPeralta@peds.uab.edu](mailto:MPeralta@peds.uab.edu)); Jones, Patrick M; Roy Heyne; Soraya Abbasi ([soraya.abbasi@uphs.upenn.edu](mailto:soraya.abbasi@uphs.upenn.edu)); Susan Hintz; Tarah Colaizy ([tarah-colaizy@uiowa.edu](mailto:tarah-colaizy@uiowa.edu)); Yvonne Vaucher; ([Deanna\\_Maffett@urmc.rochester.edu](mailto:Deanna_Maffett@urmc.rochester.edu)); ([kwynn@upa.chob.edu](mailto:kwynn@upa.chob.edu)); Aasma Chaudhary

([aasma.chaudhary@uphs.upenn.edu](mailto:aasma.chaudhary@uphs.upenn.edu)); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby ([cathy.grisby@uc.edu](mailto:cathy.grisby@uc.edu)); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale ([ehale@emory.edu](mailto:ehale@emory.edu)); Fortney, Christine; Gauldin, Cheri,; Mcdavid, Georgia E; Holly\_Wadkins@urmc.rochester.edu ([Holly\\_Wadkins@urmc.rochester.edu](mailto:Holly_Wadkins@urmc.rochester.edu)); Joanne Finkel; Karen Johnson ([karen-johnson@uiowa.edu](mailto:karen-johnson@uiowa.edu)); Kimberley Fisher; Leslie Wilson; Lijun Chen ([Lijun.Chen@UTSouthwestern.edu](mailto:Lijun.Chen@UTSouthwestern.edu)); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen ([Rosemary\\_Jensen@urmc.rochester.edu](mailto:Rosemary_Jensen@urmc.rochester.edu)); Stephanie Wiggins; Teresa Chanlaw ([tchanlaw@mednet.ucla.edu](mailto:tchanlaw@mednet.ucla.edu)); Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** Slides addressing support

If you are asked to discuss/present/defend SUPPORT, some of the slides in the last part of this talk given at Emory last week may save you some trouble preparing slides. Some of you might also be interested in some of the thoughts presented ref standards for comparative effectiveness research.

**From:** Tyson, Jon E  
**To:** richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade Rich; mgantz@rti.org; "Duara, Shahnaz" (SDuara@med.miami.edu); nfiner@ucsd.edu; moshea@wfuibmc.edu; "Phelps, Dale"; Laroja, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhaskallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; Higgins, Rosemary (NIH/NICHD) [E]; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena (bsood@med.wayne.edu); Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6)@aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira.adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichji@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yoltan; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Jones, Patrick M; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna Maffett@urmc.rochester.edu); (kwyynn@upa.chop.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gaudin, Cheri; McDavid, Georgia E; Holly Wadkins@urmc.rochester.edu (Holly Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary.Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Slides addressing support  
**Date:** Thursday, November 07, 2013 10:41:21 AM  
**Attachments:** CER Emory for NRN.pptx

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# *Science and Ethics in Comparative Effectiveness Research, QI and a Learning Health Care System*

**Jon Tyson, MD, MPH**

**Michele Bain Distinguished Professor**

**of Medicine and Public Health**

**Vice Dean for Clinical Research**

**and Healthcare Quality**

**UT Houston**

# A Clinical Scenario, 2009

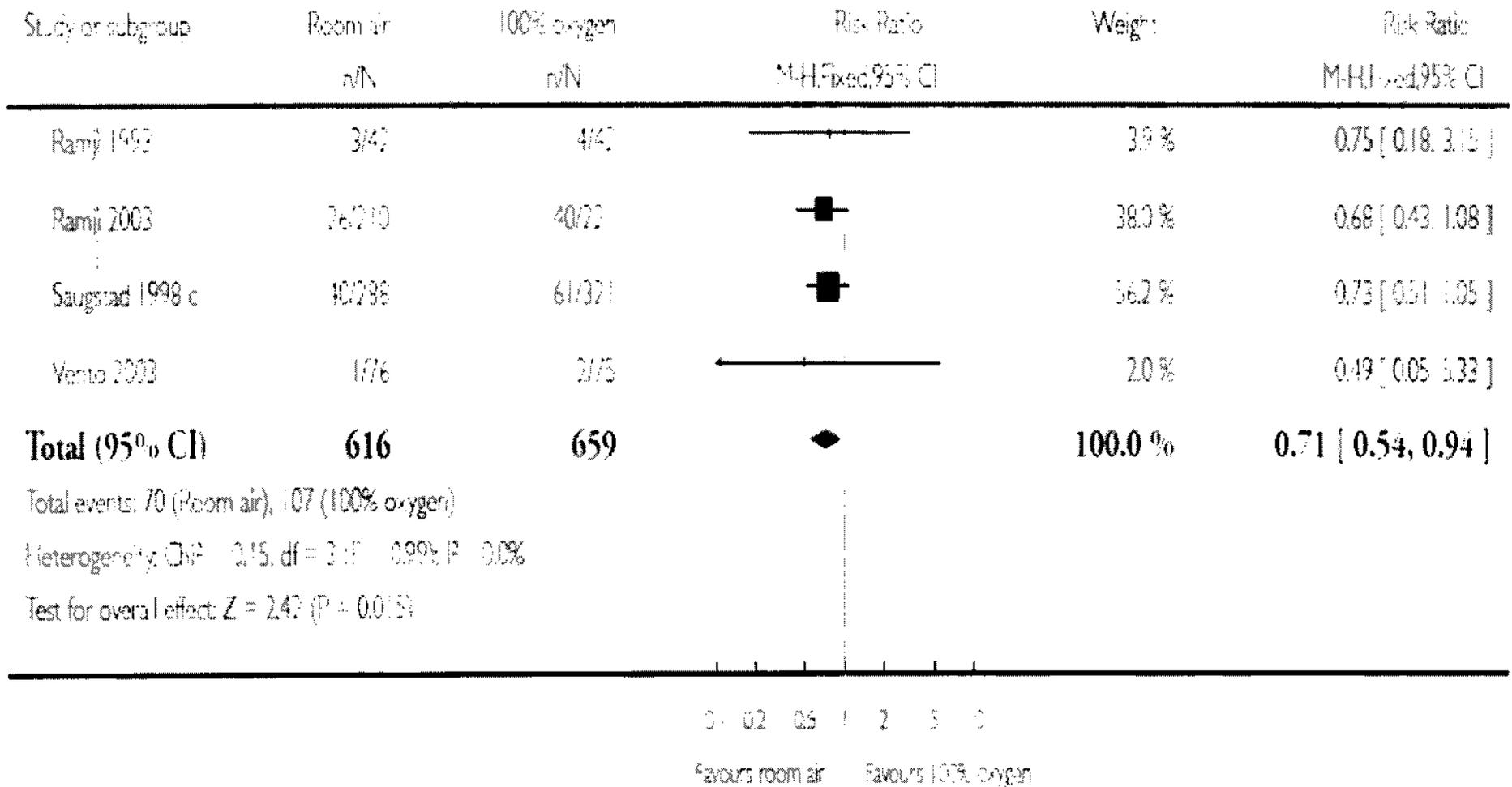
Dr. Smith, an obstetrician in a major center, performs an emergency C. section for fetal distress at 38 wks gestation. The infant has a heart rate of 40 at birth and is immediately resuscitated with 100% oxygen by Dr. Jones, the neonatologist on duty .

Later that day Dr. Smith delivers a 27 wk infant who cries at delivery. Dr. Smith immediately clamps the umbilical cord and hand the baby to Dr. Jones who promptly transports the infant to the NICU. The infant's inspired oxygen concentration is adjusted with a goal of maintaining 91-95% saturation.

Resuscitation with 100% oxygen and early cord clamping have been recommended and used for more than four decades. An oxygen saturation goal of 91-95% has been used in many NICUs for two decades. No thought is given to discussing these therapies with the parents or seeking their consent.

Yet, there have been no randomized trials showing treatment benefits exceed the hazards. As for other emergent or urgent therapies, proper trials have been thwarted by difficulty meeting stringent federal regulations and IRB policies for informed consent.

# Analysis I.I. Comparison I Room air versus 100% oxygen, Outcome I Death at latest follow up.



All studies outside U.S.; 2004 publication with analyses of morbidity also suggesting oxygen toxicity.

# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

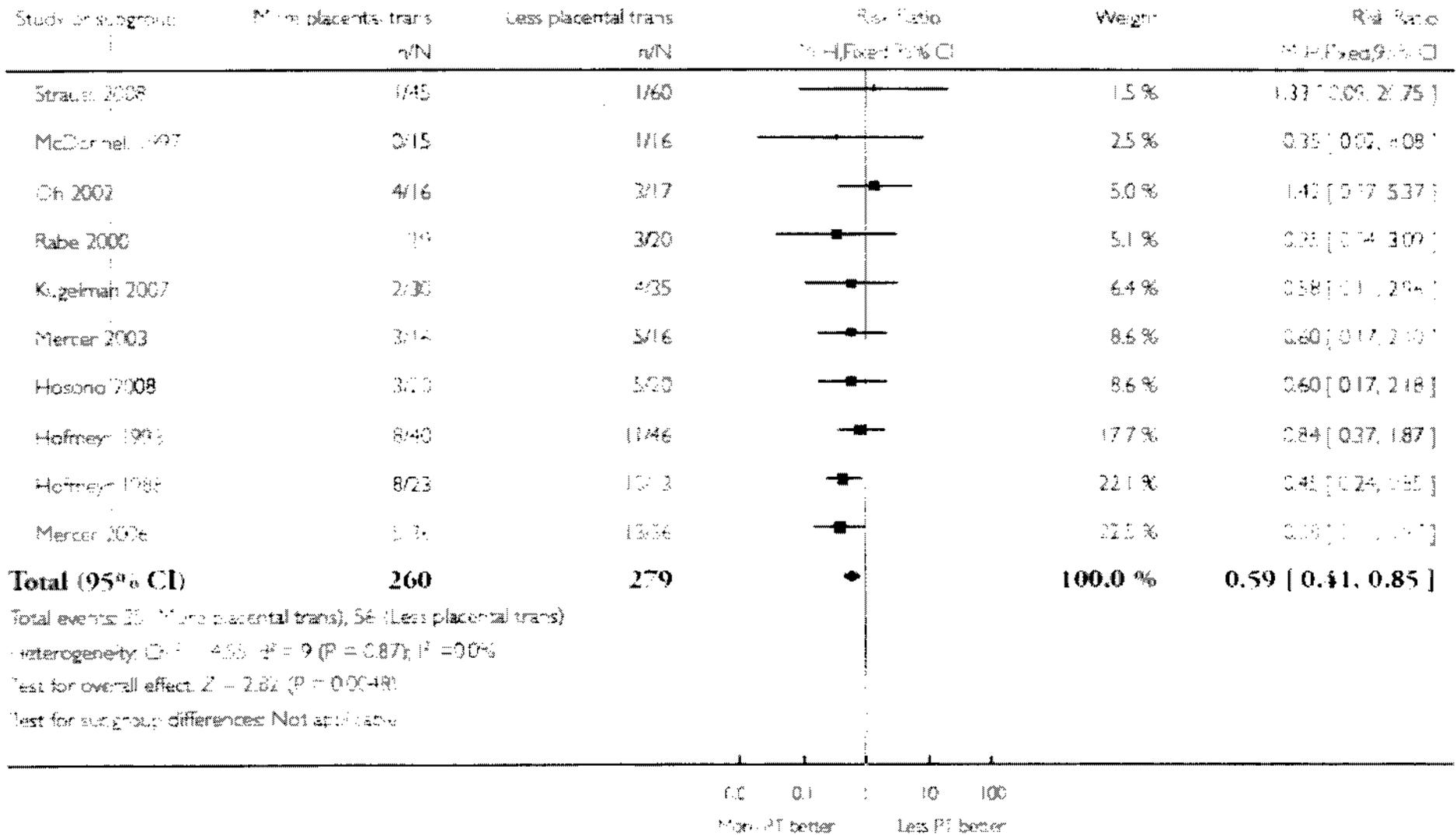


## **Part 15: Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care**

John Kattwinkel, Jeffrey M. Perlman, Khalid Aziz, Christopher Colby, Karen Fairchild, John Gallagher, Mary Fran Hazinski, Louis P. Halamek, Praveen Kumar, George Little, Jane E. McGowan, Barbara Nightengale, Mildred M. Ramirez, Steven Ringer, Wendy M. Simon, Gary M. Weiner, Myra Wyckoff and Jeanette Zaichkin

Published in 2010, these were first official recommendations to routinely resuscitate term infants using room air or blended oxygen. Research needed to determine how best to tailor  $FiO_2$  to infant's needs to optimize outcome.

**Analysis 1.21. Comparison 1 More placental transfusion (delayed clamping) versus less placental transfusion (early clamping), Outcome 21 Intraventricular haemorrhage (all grades).**



30-60 sec. delay also found to reduce transfusions. Potential hazard of increasing serum bilirubin and neurotoxicity.



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

# COMMITTEE OPINION

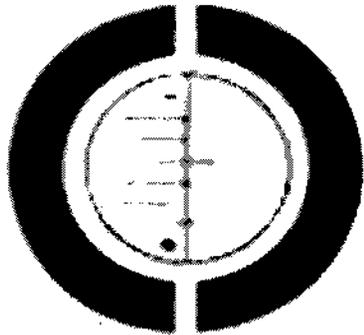
Number 543 • December 2012

## Committee on Obstetric Practice

*This Committee Opinion was developed by the Committee on Obstetric Practice with the assistance of the American Academy of Pediatrics and Tense Raju, MD, DCH, FAAP. The American Academy of Pediatrics endorses this document. This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

## Timing of Umbilical Cord Clamping After Birth

Evidence exists to support delayed umbilical cord clamping in preterm infants when feasible....Large clinical trials are needed to investigate the effect of delayed umbilical cord clamping on infants less than 28 weeks gestation



# The Cochran Collaboration

Working together to provide the best evidence for health care

Despite all the funding provided for research over many decades, the great majority of systematic reviews conclude that the available evidence from clinical trials does not allow clear conclusions about commonly used therapies. Primary problem is a lack of comparative effectiveness research assessing these therapies.

# Practice Guidelines of American College of Cardiology and American Heart Association

- **11% Level A evidence** (recommendation based on multiple RCTs or meta-analyses)
- **53% Level B evidence** (rec. based on single RCT or cohort/case control studies)
- **46% Level of evidence C** (rec. based on expert opinions, case series, etc.).

*\*Tricoci et al. JAMA 2009;301:431-41.*

# Many Therapies Widely Used Before Tested and Shown Ineffective or Harmful in RCTs

- Radical mastectomy for localized breast cancer
- Gastric freezing for ulcers
- Carotid bypass surgery to prevent stroke
- Bone marrow transplantation for metastatic breast cancer
- Antiarrhythmic drugs to prevent death after MI
- Lung volume reduction surgery for emphysema
- Vioxx to treat pain
- Pulmonary artery catheters for ICU patients
- Epoetin to achieve normal Hb with renal failure
- Bone cement for treating osteoporotic spinal fractures
- Electronic fetal heart rate monitoring to prevent fetal death and cerebral palsy
- *etc., etc., etc.*

*Effectiveness and cost  
effectiveness of everyday  
clinical practice?*

SPECIAL ARTICLE

# The Oregon Experiment — Effects of Medicaid on Clinical Outcomes

Katherine Parker, M.D., Sarah E. Taubman, M.D., David A. Asch, Ph.D.,  
David Bernheim, M.D., Jonathan G. Gruber, Ph.D., and Paul W. Koseoff, Ph.D.  
David Schneider, M.D., and Arthur J. Altmann, M.D.  
University of Washington, PI E. Health Care Health Study Group

2008 Lottery to expand Medicaid; 6387 adults selected to allow them to apply for Medicaid coverage and 5842 adults not selected were followed for 2 yrs --in effect, a randomized trial of providing access to Medicaid to low income adults

- Chances of Medicaid enrollment increased only 25%. Observed differences multiplied by 4 to assess Medicaid participation, violating intention to treat principle causing biases likely to exaggerate benefits of Medicaid participation.
- Even so, no significant benefit for many outcomes. Benefit from depression screening in unblinded and potentially biased assessments. Other benefits of questionable value. Most convincing: prevention of financial catastrophe due to healthcare costs.
- Disappointing clinical findings despite high costs may be partly due to relatively short study. However, findings like those prior Rand Healthcare Experiment, with Rx underuse, overuse, & misuse.

# How Will We Get Better?

Advances in:

- Comparative effectiveness research
- Quality improvement strategies
- Learning healthcare system

# Comparative Effectiveness Research (CER)

*As defined by Institute of Medicine:* The generation and synthesis of evidence that compares the benefits and harms of alternative methods to diagnose, treat, and monitor or improve the delivery of care.

# Key words/concepts:

- Generation AND synthesis: primary research) AND systematic reviews  $\pm$  meta-analysis;
- Effectiveness (usual clinical circumstances)--*not* efficacy (ideal or restricted circumstances);
- Alternative methods: interventions actually used in practice; “head to head” comparisons);
- Purpose (*new*): to assist consumers, clinicians, purchasers, and policy makers to make informed decisions at both individual and population level.

**The American Recovery and Reinvestment Act provided \$1.1 billion to NIH, AHRQ, HHS and new Patient Centered Outcome Research Institute.**



*The* **NEW ENGLAND JOURNAL of MEDICINE**  
**The Patient-Centered Outcomes Research Institute —  
Promoting Better Information, Decisions, and Health**

A. Eugene Washington, M.D., and Steven H. Lipstein, M.H.A.

**Private, non-profit entity with ~ \$500 million funding/yr by 2015 to conduct research to provide info. to help patients and providers make more informed decisions. Patient-centered outcomes research = Patient centered CER.**

# How to Use an Article About Quality Improvement

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Eddy Fan, MD

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Andreas Laupacis, MD, MSc

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Peter J. Pronovost, MD, PhD

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Gordon H. Guyatt, MD, MSc

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Dale W. Needham, MD, PhD

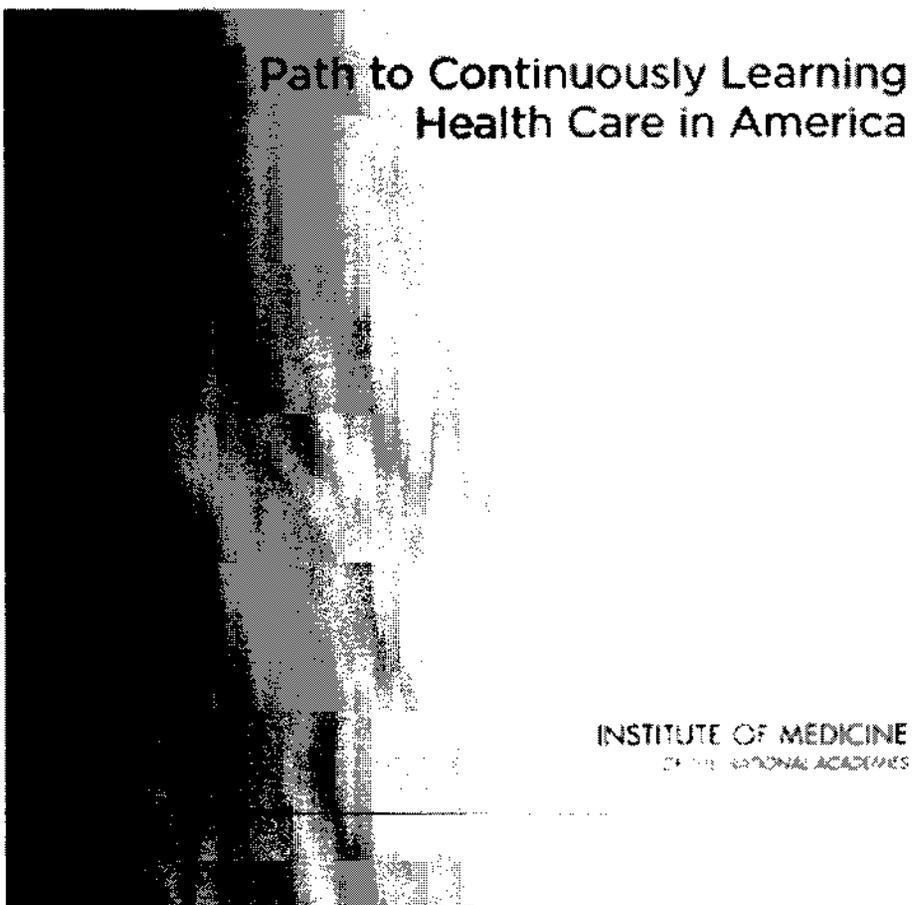
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Quality improvement (QI) attempts to change clinician behavior and, through those changes, lead to improved patient outcomes. The methodological quality of studies evaluating the effectiveness of QI interventions is frequently low. Clinicians and others evaluating QI studies should be aware of the risk of bias, should consider whether the investigators measured appropriate outcomes,

*A major criterion: Were patients randomized? If not, did investigators use an alternative design that minimizes the risk of bias?*



BEST CARE AT LOWER COST



Path to Continuously Learning  
Health Care in America

INSTITUTE OF MEDICINE  
OF THE NATIONAL ACADEMIES

“Building knowledge  
development and  
application into each  
stage of... healthcare...”

# An Ethics Framework for a Learning Health Care System: *A Departure from Traditional Research Ethics and Clinical Ethics*

BY RUTH R. FADEN, NANCY E. KASS, STEVEN N. GOODMAN, PETER PRONOVOST,  
SEAN TUNIS, AND TOM L. BEAUCHAMP

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The framework we propose...rejects the assumption that clinical research and practice [and QI] are, from an ethics standpoint, fundamentally different enterprises (Hastings Center Rep, 2013).

“The practice of medicine refers to ...activities designed solely to enhance the well-being of an individual patient...”

“Research refers to ...activities designed to develop or contribute to generalizable knowledge.”

R. Levine, Ethics and Regulation  
of Clinical Research, 2<sup>nd</sup> Edition

# **The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?**

**Elizabeth O Lillie<sup>1,2</sup>, Bradley Patay<sup>1,2</sup>, Joel Diamant<sup>1,2</sup>, Brian Issell<sup>1,2</sup>, Eric J Topol<sup>1,2,3,4</sup>, and Nicholas J Schork<sup>1,2,3,†</sup>**

**Individualizing the treatment of hypertension  
in adolescents using n-of-1 trials.  
Joyce Samuel, MD, MS, KL2 Scholar**

# The Research-Treatment Distinction: *A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*

BY NANCY E. KASS, RUTH R. FADEN, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS,  
AND TOM L. BEAUCHAMP

---

“There is no good evidence to support the empirical assumption that research studies as a class are more likely than clinical practice to run counter to the patients best interests. .. The labels “research” and “practice” are poor proxies for what should be our central moral concerns. .. “

“Requiring that all activities...designed to produce generalizable knowledge must undergo prior review by an ethics committee is a misplaced moral criterion... and a deep weakness in our current system “...[that] “creates disincentives to rigorous learning, *increasing the likelihood that interventions will continue to be introduced into clinical practice in the absence of scientific efforts to evaluate their effects.*”

- Prospective, single center study (Chow, Pediatrics, 2003). Decrease in sat goals from 90-98% to 83-93%: marked decrease in severe ROP (12.5% to 2.5%); trend toward greater survival.
- Prospective, multi-center, population-based cohort study of infants <28 wks (Tin, Arch Dis Child, 2001)

Saturation Alarm Targets	N	Survival	Survival with Retinopathy of Prematurity	Survival with Cerebral Palsy
70-90%	126	51.6%	6.2%	15.4%
84-95%	319	51.7%	15.8%	15.5%
88-98%	123	52.8%	27.7%	16.9%

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MAY 27, 2010

VOL. 362 NO. 21

## Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network\*

**1316 infants 24-27 wks gestation randomized to sat. targets of 85-89% or 91-95% . Blinding by offset oximeters. 1° hypothesis: Lower target range would reduce 1° composite outcome of either severe retinopathy of prematurity (ROP) or death before discharge (death as a *competing* outcome).**

# Results

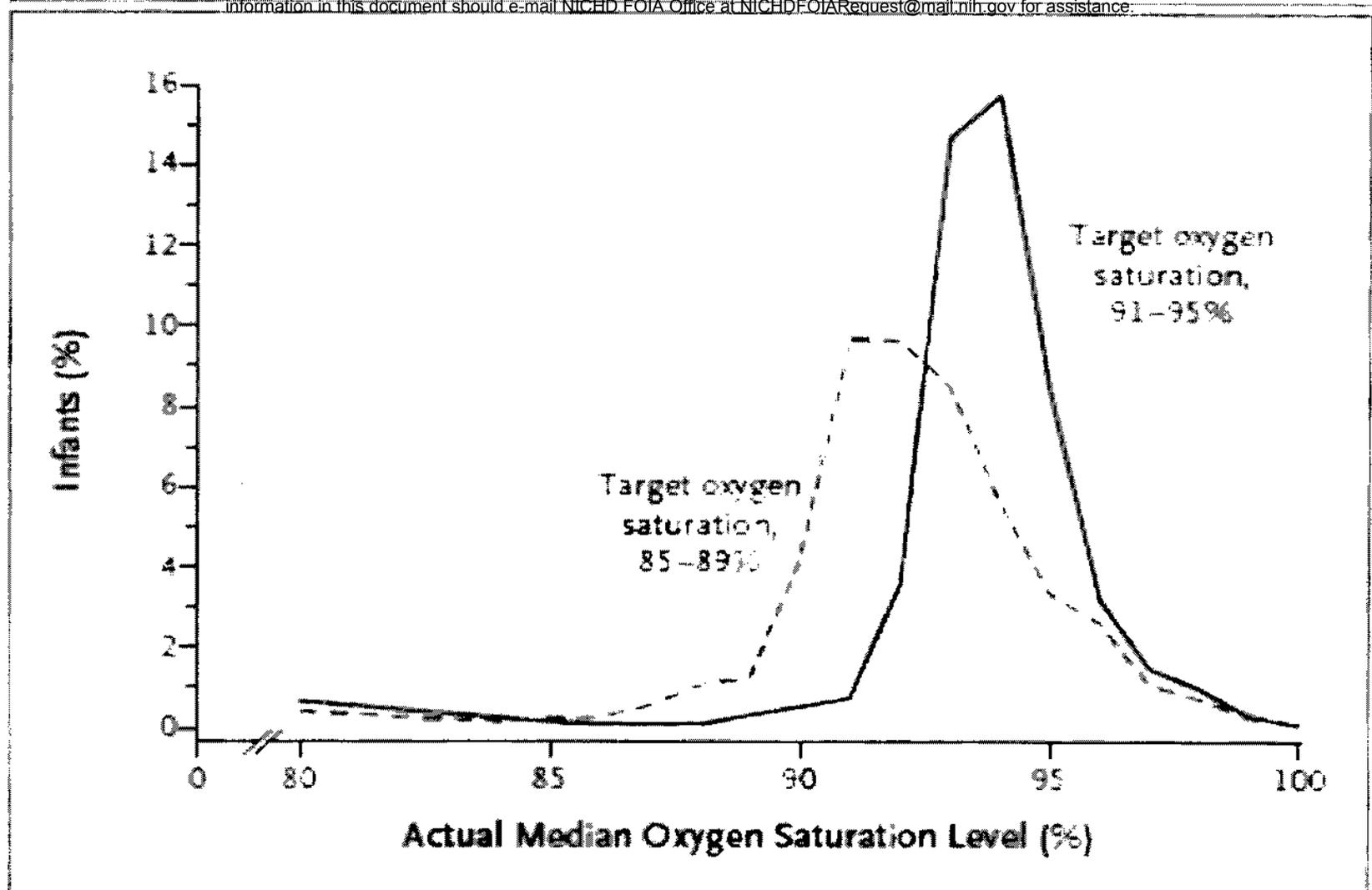
	<b>85-89% Target</b>	<b>91-95% Target</b>	<b>RR (95% CI)</b>	<b>P</b>
Severe ROP or death before discharge	28.3%	32.1%	0.90 (0.76-1.06)	0.21
Severe ROP	8.6%	17.9%	0.52 (0.37-0.73)	<0.001 NNH=11
Death before discharge	19.9%	16.2%	1.27 (1.01-1.60)	0.04 NNH=27

**Conclusion: “The increase in morality is a major concern, since a lower target range of oxygen saturation is increasingly advocated to prevent ROP.”**

# Findings at 18-22 mo.

	<b>85-89% Target</b>	<b>91-95% Target</b>	<b>RR (95% CI)</b>	<b>P</b>
<b>NDI or Death</b>	30.2%	27.5%	1.12 (0.94-1.32)	0.21
<b>Death</b>	22.1%	18.2%	1.25 (1.00-1.55)	0.046
<b>Blind both eyes</b>	0.4%	0.8%	0.54 (0.10-2.96)	0.48

Discussion: "...lower oxygen-saturation targets can not be recommended in these extremely preterm infants." N Engl J Med 2012; 367: 2495.



**Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.**

The medians of the distributions were significantly different on the basis of a rank-sum test ( $P < 0.001$ ). The 80% level of oxygen saturation shown includes all values at or below 80%.

ORIGINAL ARTICLE

# Oxygen Saturation and Outcomes in Preterm Infants

The BOONZ (United Kingdom, Australia, and New Zealand) Collaborative Groups

Sat. target of 85-89% compared to 91-95% (total n =2448) and found to increase deaths (RR=1.45 [1.15-1.84]) while reducing severe ROP (RR=0.79 [0.63-1.00]).

**CARING FOR THE  
CRITICALLY ILL PATIENT**

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ONLINE FIRST

# Effects of Targeting Higher vs Lower Arterial Oxygen Saturations on Death or Disability in Extremely Preterm Infants

## A Randomized Clinical Trial

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Smaller international trial (n=578) with differences in same direction for death (OR=1.08) and ROP (0.85) though  $p > 0.05$ . Apparently tighter sat curves.

March, 2013: Office of Human Research Protections (**OHRP**) notifies UAB (center of PI for SUPPORT) that the trial had violated regulatory requirements for informed consent, claiming that consent form should have stipulated that SUPPORT involves substantial risks” and that “the level of oxygen provided to some infants could increase risk of brain injury or death.”

Death not specified because not considered a risk.

Model consent form: The benefit of higher versus lower levels of oxygenation in infants, particularly premature infants is not known.

UTH consent form: The use of lower saturation ranges may result in a lower risk of ROP and BPD. However oxygen saturations which are too low may result in poor neurological outcomes such as learning disabilities and muscle movements. Currently there is no agreement on the accepted saturation ranges...”””

OHRP letter included multiple erroneous statements and misinterpretations. No apparent consultation with any IRB members, neonatologists, or clinical trialists.

April 2013. Public Citizen, a nonprofit advocacy group (Michael Carome, deputy director formerly at OHRP), sent letter to HHS director claiming that the parents were deliberately misled and that enough was known that any study comparing the two target levels of oxygen saturation would be both unethical and not compliant with HHS regulations.”

Demanded that HHS and NIH issue a public apology to parents and that other Network trials be stopped

Public Citizen Litigation files a law suit against UAB.

## **The New York Times**

April 10, 2013

# **Study of Babies Did Not Disclose Risks, U.S. Finds**

By **SABRINA TAVERNISE**

A federal agency has found that a number of prestigious universities failed to tell more than a thousand families in a government-financed study of oxygen levels for extremely premature babies that the risks could include increased chances of blindness or death.

None of the families have yet been notified of the findings from the Office for Human Research Protections, which safeguards people who participate in government-financed research. But the agency's conclusions were listed in great detail in a letter last month to the University of Alabama at Birmingham, the lead site in the study. In all, 23 academic institutions took part, including Stanford, Duke and Yale.

## **The New York Times**

April 15, 2013

# **An Ethical Breakdown**

By **THE EDITORIAL BOARD**

Despite reforms to protect patients from being harmed by medical research in recent decades, 23 academic institutions authorized a research project that failed to meet the most basic standard: providing an informed consent document to parents that accurately described the risks and benefits of the research to be conducted on extremely premature babies.

CORRESPONDENCE



## The OHRP and SUPPORT — Another View

The determination of ORHP ...was justified and did not overreach. Macklin and 44 other signatories (41 PhDs or JDs)



# The NEW ENGLAND JOURNAL of MEDICINE



## Perspective

### In Support of SUPPORT — A View from the NIH

Mark A. Hudson, PhD, Alan E. Guttmacher, MD, and Francis S. Collins, MD, PhD

N Engl J Med 2013; 368:2346-2351 | June 13, 2013 | DOI: 10.1056/NEJp1308897

**This controversy has...confused the research community and befuddled IRBs...The outcome ...could affect how we conduct...critical research ..for all diseases and conditions.”**

OHRP is asking that research be describe as riskier than it ...is and suggesting that parents were duped into enrolling their frail infants into dangerous research. Not only is that no true but it poses substantial risk to the conduct of valuable CER ..for the general public who....face too many treatments where uncertainty prevails about what is best.

Magnus and Caplan, Stanford and NYU

The OHRP investigation has had the effect of.... casting a pall over... clinical research to answer important questions in daily practice.

Drazen, Soloman, and Greene, NEJM

## Aug. 2013 OHRP Meeting

Often voiced misconceptions obvious to any persons knowledgeable about both research & neonatal care.

*Misconception 1. Infants died because they participated.*

	Mortality
SUPPORT 91-95% Target Group	16.2%
SUPPORT 85-89% Target Group	19.9%
Historical Reference Group	23.1%
Concurrent Eligible Not Enrolled in SUPPORT	24.1%

Participation in trial might well have improved infant care because of greater attention to regulating  $\text{FiO}_2$ .

*Misconception 2. The investigators knew--or should have known--that mortality would be higher with an oxygen sat. goal of 85-89% than 90-95%*

This misconception was based on studies conducted 5 decades ago when  $\leq 50\%$  oxygen administered. Cochrane reviews (2001, 2009): Optimal target range for blood oxygen levels has not been determined.

Too much as well as too little oxygen can increase mortality. Best prior evidence gave no indication of higher mortality at 85-89% than at 91-95% sat goals.

Even with data in hand in 3 interim “looks,” the DSMB continued RCT to end.

**Misconception 3. The inclusion of death in the primary outcome indicates that the investigators expected an effect on death.**

- High-risk patients often die without opportunity to have the outcome the Rx is hypothesized to decrease.

- Even when no effect of the Rx on death is hypothesized or plausible, often desirable to have a the 1° composite outcome that includes death, e.g. death or MI.

## Reasons for including death:

- A. Excluding any patients, particularly deaths, after randomization in CE trial may cause baseline differences between groups, violates intention to treat principle for analysis of CE studies, and may confound results.
- B. Inclusion of death in 1<sup>o</sup> outcome particularly fortunate if unexpected results obtained, e.g., in trial of intensive glucose lowering in diabetics, MI was reduced but death was unexpectedly increased.

***Misconception 4. Infants were denied the advantage of individualized saturation goals. A 3<sup>rd</sup> group given usual care should have been included. (Also used by Public Citizen in demand to stop ongoing TOP trial).***

**No data to support individualized goals.**

**Adding a 3<sup>rd</sup> group with sat. goal of 85-95% likely to produce outcomes intermediate between 85-89% and 91-95% groups and would have**

- greatly increased study costs and effort**
- delayed start of next important study**
- delayed by >2 yrs study completion and report of higher mortality with lower saturation goal.**

## *Basic questions of broad importance for CER and QI prompted by SUPPORT and by ORHP*

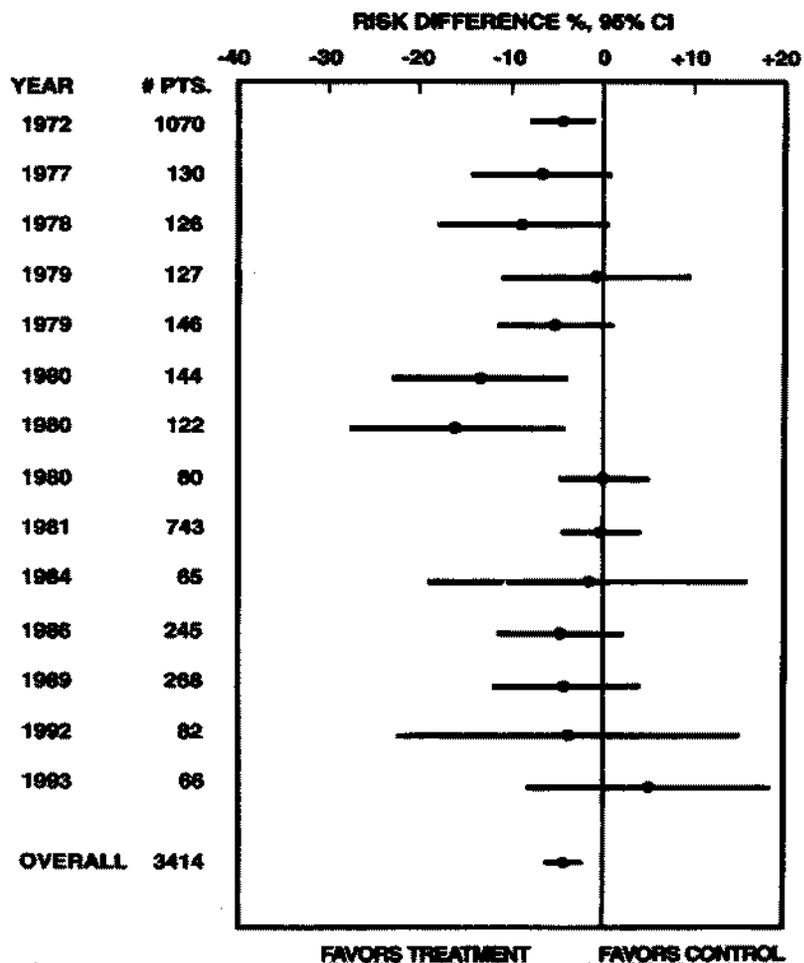
### *1. How should an IRB assess risk of standard care interventions assessed in CER or QI initiatives?*

Our suggestions (Tyson, Lantos, Kennedy, Wootton):

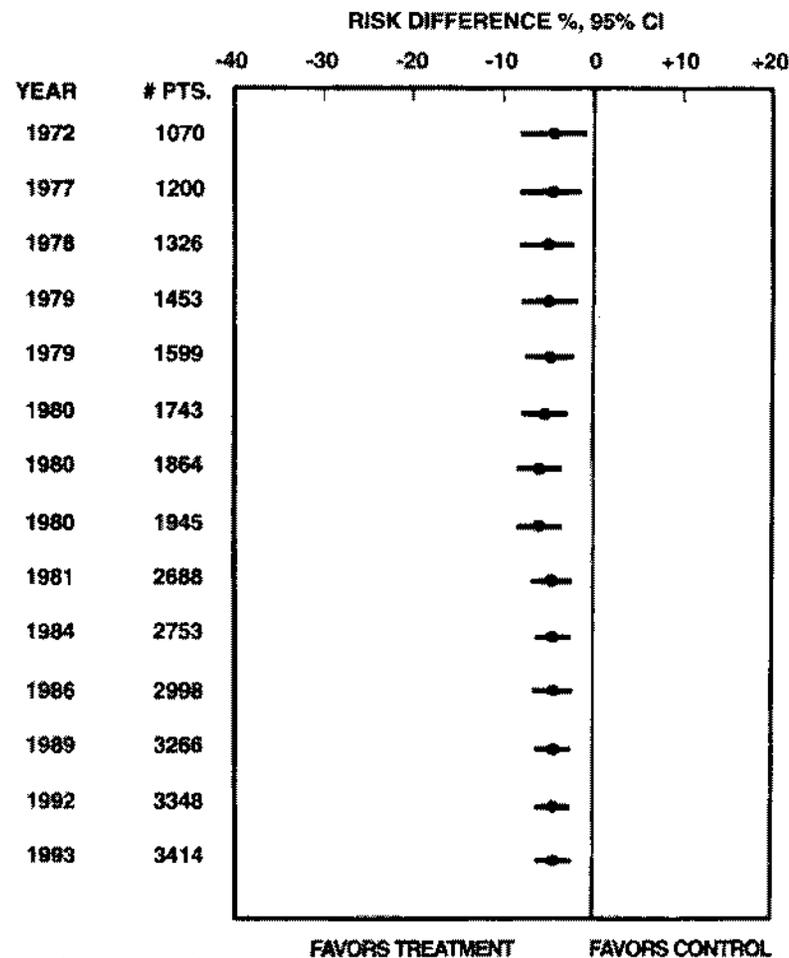
- Use “standard care” only for proven interventions (by GRADE, US preventive Task Force criteria or for practice guidelines, AGREE II criteria). Refer to other therapies as “usual” or “conventional care.”
- Carefully assess if trial is justified. Therapies beneficial in efficacy trials warrant testing in effectiveness trials. Even therapies beneficial in effectiveness trials may require further trials to assess cost effectiveness.

# Occasionally trials may be proposed that are not needed.

**EFFECT OF ANTENATAL STEROID ON NEONATAL DEATHS**



**EFFECT OF ANTENATAL STEROID ON NEONATAL DEATHS: CUMULATIVE META-ANALYSIS**



- As OHRP specifies, consider only incremental risks of research (not understood by some IRB members). In legitimate CER, no reasonably foreseeable difference in overall risks (relative to benefits) based on best available evidence.
- Consider reasonably foreseeable risks to be:
  - A. biologically plausible hazards poorly assessed in clinical studies, and
  - B. hazards marginally or significantly associated with the Rx ( $p \leq 0.10-0.15$ ) in a systematic review of relevant RCTs or in the absence of such a review, in one or more RCTs or well performed cohort studies

## *Ref SUPPORT:*

- Death not reasonably foreseeable by these criteria.
- Criteria so inclusive as to require death be listed would require it to be listed for both sat. groups.
- While this would have satisfied OHRP and likely avoided lawsuit, it is unlikely that parents would have been better informed or more satisfied.
- Basic problem is that the a truly informed decision was not possible. Otherwise the trial would not have been needed.
- Parents of infants in trial clearly better informed than parents of similar infants not in trial.

## *2. Should risk disclosure be more uniform in both clinical research and clinical practice?*

Our views:

- Further study needed of such issues as:
  - factors that would augment validity of consent
  - wants, needs, and comprehension of patients/surrogates in routine and emergent circumstances;
  - effects of differing approaches to risk disclosure, including adverse nocebo effects
- Different risk disclosure in clinical trials and practice for same unproven Rx not supported by ethical principles or patient surveys.

### *3. Should randomization be considered to present a risk to subjects?*

**No, not in legitimate CE trials (when superior treatment has not been established). Reasons:**

**A. Randomization to alternative therapies has no foreseeable overall risks (relative to benefits)**

**CE trials differ from those regs developed for and have no experimental group and no control group  
Randomization does not affect Rx risks, simply a tool to avoid differences in baseline risks that cause erroneous conclusions.**

**B. When better Rx is unclear, Rx of patient depends on happenstance.**

Treatment decision at best a mental coin flip.

**C. Unfounded assumption that randomization increases risk inadvertently harms patients.**

Regulatory requirements based on this assumption inadvertently discourage proper testing and encourage clinical use of unproven therapies (*the great majority of therapies*).

4. When should an IRB be allowed to waive informed consent for research involving randomization of subjects in CE research?

Our view: *Yes*, in emergent or urgent--but not necessarily life-threatening--circumstances when valid consent can not be quickly obtained and

- requiring consent for all patients will preclude a trial of reasonable length and cost, *OR*

- requiring consent for all patients is likely to result in major selection biases, *OR*

- delays are likely to affect whether the Rx benefits or hazards for some or all patients.

# Prior Proposal in NICHD Neonatal Network to Assess Effects of Delayed Clamping on Major Adverse Outcomes in ELBW Infants

- Extremely preterm deliveries often unpredictable
- Many of mothers receive little or no prenatal care, present to L and D in advanced labor, and /or have severe complications.
- Serious effort to obtain valid consent in busy L&D units would require 24/7 in-house personnel
- Adequate power would require  $\geq 3$  y enrollment in 12 ICUs and  $\geq \$3$  million cost to obtain consent.
- Major selection biases in excluding highest risk infants if informed consent required for all.

Although federal regulations allow emergency exemption when strict requirements met, all but one Network PI agree that their own IRB would not allow exemption and that requiring consent for all would preclude a trial of reasonable effort, length, and cost that would be free of major selection biases.

It is not plausible to presume that a patient would want his physician to use an innovative therapy never properly tested for safety or efficacy ..., with no prior review, no monitoring, no post hoc review but would object to using the same treatment with all the safeguards of a controlled trial.

N. Fost

# Estimated Effect of 1 Hour Delay in CRASH 2 Trial of Tranexamic Acid in Trauma Patients

Roberts et al, Lancet 2011;377: 1071

- Logistic regression model with treatment group, time to treatment, and interaction term (to assess how treatment effect changes with time to treatment)
- Estimated Delay to obtain informed consent = 1.2 h
- Overall RR of death due to bleeding with treatment = 0.85 (0.76-0.96)
- RR with 1 h treatment delay = 0.96 (0.86-1.08)

- Requiring consent when delays expected to decrease hypothesized Rx benefits may
  - a) increase adverse outcomes
  - b) cause erroneous conclusions that adversely affect a very large number of future patients;
  - c) delay valid trial completion & dissemination of beneficial Rx or abandonment of harmful Rx.
- If use without consent acceptable in these circumstances, use without consent should also be acceptable in proper CE trial.

**Impeding research, no less than performing it, has ethical consequences.**

**Eisenberg, 1977**

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, November 06, 2013 1:31 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Cc:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** FW: On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

FYI

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Frantz, Ivan [mailto:[Ivan.Frantz@childrens.harvard.edu](mailto:Ivan.Frantz@childrens.harvard.edu)]  
**Sent:** Wednesday, November 06, 2013 1:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

I was told that if there is sufficient interest they will look into live streaming. As of now they plan to record it and link to their website. I told them that I thought there would be interest if promoted.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Wednesday, November 06, 2013 8:48 AM  
**To:** Frantz, Ivan  
**Subject:** RE: On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

Thanks for sharing – is there remote access to the meeting?  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575

**MEDICAL ETHICS**

Thursday, December 5, 2013  
4:00 P

Harvard Medical School  
MFC Room 2  
260 Longwood Avenue, Boston

# Ethical Issues in Comparative Effectiveness Research:

*Examples: the neonatal SUPPORT trial, and the use of oxygen saturations  
in premature infants*

**Ruth Macklin, PhD**

Professor Emerita, Department of Bioethics and  
Director of the Center for Health Equity Promotion and  
Prevention, Johns Hopkins University

**(Moderator) Robert Truog, MD**

Professor of Medical Ethics and Director of the Center for  
Bioethics and Director of the Center for Health Equity  
Promotion and Prevention, Harvard Medical School

**Benjamin Wilfond, MD**

Professor of Pediatrics and Director of the Center for  
Comparative Effectiveness Research, Johns Hopkins  
University

The neonatal SUPPORT trial, which randomized extremely low birth weight infants to lower or higher levels of oxygen saturation as part of their ventilator management raised ethical issues that are turning out to be among the most controversial topics in research ethics in many years.

The trial was conducted at 22 sites and involved 1300 newborns. The target oxygenation saturations between the two arms were both considered to be within the standard of care, but the consent documents either did not mention or were unclear about the risks of retinopathy of prematurity, impaired brain development, or death in the two arms of the trial.

In March 2013 OHRP issued a compliance oversight determination letter, finding that consent was deficient and violated the regulatory requirements, a judgment that could have broad implications for other forms of comparative effectiveness research. This determination generated a storm of controversy, including questions about how to assess the risks and benefits of

**“standard of care” interventions, and even whether informed consent is ethically necessary for this type of research.**

**Ben Wilfond and Ruth Macklin each first-authored opposing letters that were published in the New England Journal of Medicine, with dozens of signatories represented on each side. We are fortunate that they have agreed to come to Boston for a moderated debate on these important and interesting questions.**

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, November 06, 2013 8:45 AM  
**To:** Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** FW: On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

FYI

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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Frantz, Ivan [<mailto:Ivan.Frantz@childrens.harvard.edu>]  
**Sent:** Wednesday, November 06, 2013 7:17 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

I thought the group might be interested in this.

My email address will be changing to [ifrantz@bidmc.harvard.edu](mailto:ifrantz@bidmc.harvard.edu). Both work for now.

---

**From:** Gately, Sarah  
**Sent:** Tuesday, November 05, 2013 7:32 PM-----  
**To:** Agrawal, Pankaj; Belfort, Mandy Brown; Gorman, Terri; Grant, Ellen; Gregory, Mary; Hansen, Anne; Hossain, Tanzeema; Kourembanas, Stella; Leeman, Kristen; O'Reilly, Deirdre; Piao, Xianhua; Rhein, Lawrence; Sayeed, Sadath ; Sola-Visner, Martha; Chang, Mun Seog; Fernandez-Gonzalez, Angeles; Greer, Eric; Im, Kiho; Jeong, Sung-Jin; Jones, Stephanie; Lee, Changjin; Liu, Zhi-Jian; Luo, Rong; Mitsialis, Alex; Park, Pyong; Perrella, Mark; Shi, Yang; Takahashi Oki, Emi; Carroll, Jeanne; Cowan, Eileen; Deschmann, Eموke; Detora, Adam; Ehret, Danielle; Geha, Mayya; Ghanta, Sailaja; Hajj, Hanine; Ho, Timmy; Joung, Kyoung; Kunz, Sarah; Matute, Juan; Montenegro, Brian; Morton, Sarah; Mukhia, Amit; Ruoss, Lauren; Sajti, Eniko; Walsh, Brian (NICU-Fellow); Brodsky, Dara ; Burris, Heather; Dukhovny, Dmitry; Gray, Jim ; Gregory, Mary Lucia ; Gupta, Munish ; Litt, Jonathan; Martin, Camilia ; McCormick, Marie; Pursley, DeWayne ; Smith, Vincent ; Stewart, Jane ; Zupancic, John ; Abdulhayoglu, Elisa ; Brezinski, Donna; Chatson, Kimberlee ; Culic, Ivana; Cummings, Christy; Deno, Ceara; Doherty, Elizabeth; Fiascone, John; Frantz, Ivan; Gilson, Diana; Hossain, Shah; Hwang, Sunah; James, Philip; Knorr, Aimee; Konnikova, Liza; Kubicka, Zuzanna; Lacy, Molly; Lee, Jennifer; Maari, Nisreen; Magno, Andrea; McAlmon, Karen ; Remy, Daphne; Rousseau, Tamara; Spadafora, Ruggero; Testa, Silvia; Tran, Tai; Weinschenk, Nancy; [rwilker@partners.org](mailto:rwilker@partners.org); Zahr, Eyad  
**Subject:** On behalf of Dr. Kourembanas: 12.5.13 - Can Comparative Effectiveness Research be Ethical after SUPPORT?

Dear Colleagues,

You may be interested in this upcoming ethics debate that addresses issues related to the SUPPORT trial but has broad implications for clinical research.

Regards,

Stella



**MEDICAL ETHICS**

Thursday, December 5, 2002  
4:00 P  
Harvard Medical School  
MFC Room 2  
260 Longwood Avenue, Boston

## Ethical Issues in Comparative Effectiveness Research:

*Lessons from the SUPPORT trial: 100% vs. 90% oxygen saturations*  
November 14, 2002

**Ruth Macklin, PhD**  
Professor Emerita, Department of Bioethics  
Dr. Leavell P. Frankel Professor of Bioethics  
Baylor College of Medicine

**Benjamin Wilfond, MD**  
Professor of Pediatrics, Division of Neonatology  
University of Michigan Medical Center

**[Moderator] Robert Truog, MD**  
Professor of Pediatrics, Harvard Medical School  
Dr. Robert Truog, MD, is the Director of the Center for  
Bioethics and Health Care at the Harvard  
Medical School and the Massachusetts General  
Hospital.

**CONFERENCE**

The neonatal SUPPORT trial, which randomized extremely low birth weight infants to lower or higher levels of oxygen saturation as part of their ventilator management raised ethical issues that are turning out to be among the most controversial topics in research ethics in many years.

The trial was conducted at 22 sites and involved 1300 newborns. The target oxygenation saturations between the two arms were

both considered to be within the standard of care, but the consent documents either did not mention or were unclear about the risks of retinopathy of prematurity, impaired brain development, or death in the two arms of the trial.

In March 2013 OHRP issued a compliance oversight determination letter, finding that consent was deficient and violated the regulatory requirements, a judgment that could have broad implications for other forms of comparative effectiveness research.

This determination generated a storm of controversy, including questions about how to assess the risks and benefits of “standard of care” interventions, and even whether informed consent is ethically necessary for this type of research.

Ben Wilfond and Ruth Macklin each first-authored opposing letters that were published in the New England Journal of Medicine, with dozens of signatories represented on each side. We are fortunate that they have agreed to come to Boston for a moderated debate on these important and interesting questions.

**From:** (b)(4),(b)(6)  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** (b)(4),(b)(6)  
**Subject:** RE: Process of acquiring data  
**Date:** Monday, November 04, 2013 10:20:07 AM

---

Good morning Rose. Thank you very much for your prompt response and outline of the data request process. I really appreciate your willingness to request the steering committee for the approval. As Dr. Martin suggested, we will work on this formal request as soon as the project is funded.

Again my sincere thanks and regards to all of you for the help you have offered and the information you have shared.

With best regards, (b)(4),(b)(6)

(b)(4),(b)(6)

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, November 04, 2013 6:41 AM  
**To:** (b)(4),(b)(6)  
**Cc:** (b)(4),(b)(6)  
(kzatenka@u.wisc.edu)  
**Subject:** RE: Process of acquiring data

Hi

This request needs to go to the Steering committee, for approval, and if approved, a data use agreement (DUA) with RTI and IRB approval is required PRIOR to any use of the data. The current access that (b)(4),(b)(6) have do not cover access for studies outside of their current DUA. Please send me the proposal and I can request steering committee approval.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** (b)(4),(b)(6)  
**Sent:** Friday, November 01, 2013 12:56 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** (b)(4),(b)(6)  
**Subject:** Re: Process of acquiring data

Dear Dr. Higgins,

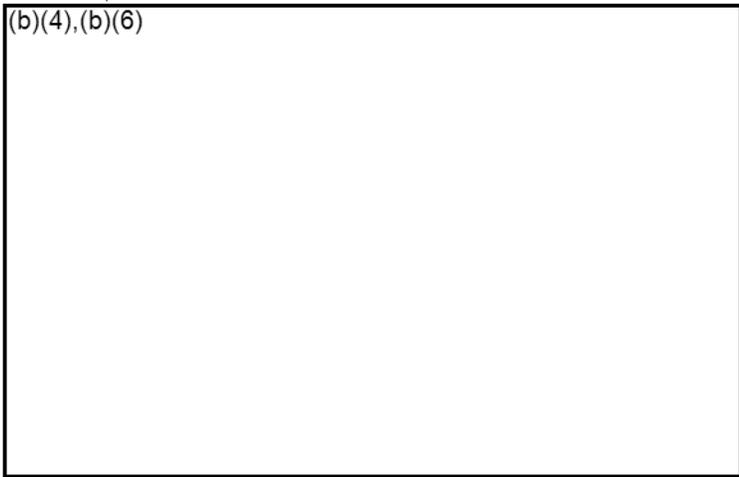
Please allow me to introduce myself. My name is Abdus Sattar and a Biostatistician. I am from Case Western Reserve University. I received your contact information from my collaborator Dr. (b)(4),(b)(6)

(b)(4),(b)(6) (cc'd to this email).

(b)(4),(b)(6)

Sincerely,

(b)(4),(b)(6)



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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Terry, Sharon MA  
**Sent:** Sunday, November 03, 2013 8:59 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Natasha Bonhomme; Tetyana Murza  
**Subject:** Re: Support group

Hi Kathy,

I am ccing Natasha because she may also know of another key group that can rally the troops for babies.

The other one I mentioned is the Partnership for Women and Families (they were key in GINA and Susannah Baruch worked for them).

Can you tell me who Tanya in my office should work with in your office to get a meeting on the books? I think it would be better at Genetic Alliance then NIH, is that your sense too?

Best,  
Sharon

-----  
Sharon F. Terry | President and CEO  
Genetic Alliance | 4301 Connecticut Ave., NW | Suite 404 | Washington, DC 20008-2369  
Phone: 202.966.5557 | Fax: 202.966.8553 | [sterry@geneticalliance.org](mailto:sterry@geneticalliance.org)

Donate: [www.geneticalliance.org/donate](http://www.geneticalliance.org/donate)  
[@sharonferry](mailto:@sharonferry) | [LinkedIn.com/in/sharonterry](http://LinkedIn.com/in/sharonterry) |  
[Ashoka.org/fellow/sharon-terry](http://Ashoka.org/fellow/sharon-terry) | [SharonTerry.com](http://SharonTerry.com)

-----  
**From:** <Hudson>, "Kathy [E] (NIH/OD)" <[Kathy.Hudson@nih.gov](mailto:Kathy.Hudson@nih.gov)>  
**Date:** Sunday, November 3, 2013 at 12:27 PM  
**To:** "Sharon F. Terry" <[sterry@geneticalliance.org](mailto:sterry@geneticalliance.org)>  
**Cc:** Alan Guttmacher <[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)>, "Devaney, Stephanie (NIH/OD) [E]" <[stephanie.devaney@nih.gov](mailto:stephanie.devaney@nih.gov)>  
**Subject:** Support group

Sharon

It was great to talk to you about your concerns about the lack of voices to support research to improve health and health care for babies.

You mentioned bringing together some folks to discuss the current situation. You mentioned aamc, families USA, family voices, and one other group (who was that?)

I would be happy to join such a meeting and I bet Alan would as well.

Thanks tons.

Kathy

**Kathy Hudson, Ph.D.**  
**Deputy Director for Science, Outreach, and Policy**  
**NIH**  
**301 496 1455**  
**[kathy.hudson@nih.gov](mailto:kathy.hudson@nih.gov)**

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, October 29, 2013 9:23 AM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Manuscript #13-551 Decision

What we have been sending to authors to include with the Acknowledgements (or wherever the journals feel is appropriate) is a statement that:

**“While NICHD staff did have input into the study design, conduct, analysis, and manuscript drafting, the comments and views of the authors do not necessarily represent the views of the NICHD.”**

Does that suffice?

Stephanie

---

Stephanie Wilson Archer  
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Monday, October 28, 2013 6:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Manuscript #13-551 Decision

Would not do it now and can definitely see what you are saying for that interpretation –thought of that too – just *food for thought for the future articles*

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
*Eunice Kennedy Shriver* National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 28, 2013 6:50 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Manuscript #13-551 Decision

Mona  
Kathleen Kennedy, the first author is really saying our data support the current AAP recs- I can see if she sent it back but it has gone through multiple rounds of review without the disclaimer

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 28, 2013, at 6:41 PM, "Rowe, Mona (NIH/NICHD) [E]" <[rowem@exchange.nih.gov](mailto:rowem@exchange.nih.gov)> wrote:

Hi Rose – I tried calling you today – and decided not to leave you a message – totally my fault and my apologies for getting back to you earlier

If it is not too late – probably best to (b)(5)

(b)(5)

THAT SAID IF IT IS TOO LATE THAN EVERYTHING IS STILL FINE – JUST SOMETHING TO THINK ABOUT IN THE FUTURE

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 1:16 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Manuscript #13-551 Decision

There is no disclaimer- let me know if one is needed

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 12:47 PM, "Rowe, Mona (NIH/NICHD) [E]" <[rowem@exchange.nih.gov](mailto:rowem@exchange.nih.gov)> wrote:

Okie doke—so much for growing old and neuronal connections – probably spoke about a disclaimer previously

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 10:18 AM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Manuscript #13-551 Decision

Clearance was done months ago

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

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MSC 7510

Bethesda, MD 20892

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301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Rowe, Mona (NIH/NICHD) [E]

**Sent:** Monday, October 21, 2013 10:17 AM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Manuscript #13-551 Decision

Hi Rose - -have not gone into the clearance system yet to see if it there for review—and will look at the article—one thing before even reading it - -if in anyway it (b)(5)

(b)(5)

*Mona*

Mona Jaffe Rowe, M.C.P.

Associate Director for Science Policy,

Analysis and Communication

*Eunice Kennedy Shriver* National Institute of

Child Health and Human Development

National Institutes of Health, DHHS

Building 31, Rm 2A-18

31 Center Drive

Bethesda, MD 20892-2425

Phone: 301.496.1877/Fax: 301.496.0588

Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

---

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

**Sent:** Monday, October 21, 2013 9:15 AM

**To:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** FW: Manuscript #13-551 Decision

Bob and Mona

As a heads up, This secondary study from the SUPPORT trial has been provisional accepted for the Journal of Perinatology. We looked at the eye exams done as part of the SUPPORT trial to evaluate the current recommendations from the AAP to guide physician practice. The data from the SUPPORT trial show that the eye exam recommendations are current, should not be changed, but close follow up after discharge is warranted for infants who go home with either active disease or immature blood vessels in their retina.

Let me know if you need more information. Dr. Kennedy will provide us with the galley proofs when she gets them.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, October 11, 2013 12:58 PM  
**To:** [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org))  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Manuscript #13-551 Decision

Here's the provisional email acceptance from J Perinatol. There aren't any substantive criticisms. I've attached a drafted response letter. There were very few changes made to the manuscript (highlighted in yellow). Many of the suggestions either didn't make sense to me or were asking for adding things that were already there. I tried to be diplomatic in the response (also attached) – mostly just specifying where the information is. Let me know if you have suggestions or if you understand any of the suggestions better than I did. I've attached the previously submitted and updated versions of the manuscript for you to compare if you want.

I'm not sure I understand what the reviewer is trying to say in #15 but, as I look at these numbers again (last row in Table 4), I don't think they make an important point. I think we should take them out of this table and count them differently in the text if we're going to include them. I think [redacted] was trying to make the point that babies are more likely to have onset of severe ROP after discharge home if they have been back transferred to a lower acuity NICU. Is that right? To look at that, we really need denominators for infants who were and were not back transferred to a lower acuity NICU before discharge home. Then we could calculate the proportion of each who had onset of severe ROP after discharge home. It gets kind of messy because some infants who were back transferred probably had final ROP outcome determined before back transfer and they don't really belong in either group.

[redacted] could you please add "Gestational Age in Completed Weeks" to the x-axis for the most recent version of Figure 2? I've added the "Any ROP" to Table 2 by copying it from a prior iteration of the manuscript. Could you please verify that the numbers are correct? I also have a question for you in the comment in the revision.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program

UT-Houston Medical School

6431 Fannin, Suite 2.106

Houston, TX 77030

713 500-6708

**From:** [jperinatol@us.nature.com](mailto:jperinatol@us.nature.com) [<mailto:jperinatol@us.nature.com>]

**Sent:** Monday, September 23, 2013 10:17 AM

**To:** Kennedy, Kathleen A

**Subject:** Manuscript #13-551 Decision

22nd Sep 2013

Dear Dr. Kennedy:

Manuscript #: 13-551

Title: Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants

Author: Dr Kennedy

The initial review of your manuscript is complete. I am happy to inform you that the manuscript may be accepted for publication if it is revised extensively according to our suggestions. Below are the reviewers' comments that indicate their concerns. Both reviewers were enthusiastic about the manuscript, one provides numerous suggestions for improvement.

In addition I would appreciate how the manuscript may be shortened in its print version by converting some of the Tables or the Acknowledgement to Supplementary Materials. The three page single spaced listing of the institutions and various committees would consume 4 print pages and seems especially eligible to be fine for electronic only publication. If supplied as Supplemental Materials it would still be available to all readers - since most readers will download the text from electronic sources they can easily also receive the supplemental material.

Within the next three months, please resubmit the revised manuscript online together with a summary of your responses to the reviewer comments. Be sure to include your Conflict of Interest statement in the manuscript. The manuscript will be read within the office and then may be resent to the outside reviewers for further evaluation.

If we do not receive the revised manuscript within three months the file will be closed and any subsequent resubmission would be treated as a new manuscript. Please notify us should you decide to withdraw the manuscript from further consideration.

Click on the link below to submit the revision online (or highlight, copy and paste all the information between the <> symbols).

<http://mts-jper.nature.com/cgi-bin/main.plex?el=A1BX7CFI6A7Bmw3J6A9sMZv4iLf6KzPt9u7LQJXQZ>

Thank you for submitting this paper to the Journal of Perinatology.

Sincerely,

Edward E. Lawson, M.D.  
Editor-in-Chief  
the Journal of Perinatology  
Johns Hopkins Medicine  
600 N. Wolfe St  
Baltimore, MD 21287

---

**Reviewer #1 (Comments to the Author):**

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer #2 (Comments to the Author):

(b)(4),(b)(6)

This email has been sent through the NPG Manuscript Tracking System NY-610A-NPG&MTS

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**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: NIH Health Care System Research Collaboratory - request for you to present at Grand Rounds  
**Date:** Monday, October 28, 2013 8:20:26 PM

---

Rose.

Ok. Will do it.

Wally

-----Original message-----

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**To:** "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>  
**Sent:** Mon, Oct 28, 2013 22:32:14 GMT+00:00  
**Subject:** Re: NIH Health Care System Research Collaboratory - request for you to present at Grand Rounds

Wally  
Up to you- a scientific presentation on the support trial would be good

Rose

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 28, 2013, at 5:18 PM, "Wally Carlo, M.D."  
<[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)<<mailto:WCarlo@peds.uab.edu>>> wrote:

Hi Rose:

Rob Califf called me about this conf call. He would like me to give an update on SUPPORT. See below. I was reluctant to do it initially but Rob and others in this group have been very supportive so I wanted to do it but wanted to check with you.

Let me know what you think.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 4004

From: Cheri Janning [<mailto:cheri.janning@duke.edu>]

Sent: Monday, October 14, 2013 11:19 AM  
To: Wally Carlo, M.D.  
Cc: Robert Califf, M.D.; Tammy Reece  
Subject: NIH Health Care System Research Collaboratory - request for you to present at Grand Rounds

Dear Dr. Carlo,

I work with Dr. Califf on the NIH HCS Collaboratory and we invite you to speak at the NIH Collaboratory Grand Rounds webinar that is held every Friday from 1-2pm (eastern). The presentations are 30 minutes followed by 30 minutes of moderated discussion. We would like your presentation to provide an update on the SUPPORT Trial. We have dates available in the coming months and hope your calendar will allow you to participate.

This link will take you to prior Grand Rounds presentations:  
<https://www.nihcollaboratory.org/Pages/Forms/Grand-Rounds.aspx>

I would be happy to answer any questions you may have.

Many thanks for considering our speaking request.

Best,

Cheri Janning, RN, BSN, MS  
Program Director, NIH HCS Collaboratory Coordinating Center  
Senior Clinical Project Manager, Clinical Trials Transformation Initiative (CTTI)  
Duke Translational Medicine Institute  
Office: (919) 668-8374  
e-mail: [cheri.janning@dm.duke.edu](mailto:cheri.janning@dm.duke.edu)<<mailto:cheri.janning@dm.duke.edu>>

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Hot Topics  
**Date:** Monday, October 28, 2013 2:23:45 PM

---

THX!

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: (b)(6)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, October 28, 2013 12:41 PM  
**To:** Abhik Das (adas@rti.org); Wally Carlo, M.D.  
**Subject:** FW: Hot Topics

Abhik  
Here is the attachment

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, October 28, 2013 1:25 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie  
**Subject:** FW: Hot Topics

Hi Rose, Neil, and Marie:

One of the concerns of how we reported O2 sat distribution in SUPPORT is that we used median sat

per baby rather than % of time at each oxygen saturation.

Enclosed is the BOOST II paper. See how they reported their O2 sat data on Figure 1. Can we get our analysis done that way for Hot Topics? Ben thinks we could compare better O2 separation that way.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 4004

---

**From:** Stenson, Ben [<mailto:Ben.Stenson@nhslothian.scot.nhs.uk>]  
**Sent:** Monday, October 28, 2013 12:19 PM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: Hot Topics

Yes.

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** 28 October 2013 17:17  
**To:** Stenson, Ben  
**Subject:** RE: Hot Topics

Hi Ben:

Do you mean to report it as you did in your Fig 1 with average % of time spent by infants at each saturation?

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
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Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: (b)(6)

**From:** Stenson, Ben [<mailto:Ben.Stenson@nhslothian.scot.nhs.uk>]  
**Sent:** Monday, October 28, 2013 11:59 AM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: Hot Topics

Hi Wally

It appears that there are still important differences of view about the effect of the different oximeters on saturation. Did you find out whether you would be able to show the saturation distributions of your Support babies in the same way that was done in BOOST as well as in the way that you did in the support paper so that there is a comparison that goes beyond the median sats histograms?  
Ben

\*\*\*\*\*

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\*\*\*\*\*

**From:** Wally Carlo, M.D.  
**To:** [adas@rti.org](mailto:adas@rti.org); Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie  
**Subject:** RE: Hot Topics  
**Date:** Monday, October 28, 2013 2:09:59 PM

---

It can wait until after the PAS deadline.

I think the analysis is straightforward.

Wally

-----Original message-----

**From:** "Das, Abhik" <[adas@rti.org](mailto:adas@rti.org)>  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>, "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>, "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>, "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>  
**Sent:** Mon, Oct 28, 2013 17:34:31 GMT+00:00  
**Subject:** RE: Hot Topics

Yes, Marie is out at least through the middle of November, and Lisa, my back up SUPPORT statistician is also pretty tied up with the Neuroimaging secondary analyses. So, this may have to wait until Marie gets back.

Wally: Can you send me the paper as well?

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, October 28, 2013 1:31 PM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil; Gantz, Marie; Das, Abhik  
**Subject:** RE: Hot Topics

Wally – I think Marie is still on (b)(6) – I have included Abhik –  
How much is involved in this analysis?

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research  
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Pregnancy and Perinatology Branch  
NIH  
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301-435-7909  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, October 28, 2013 1:25 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie  
**Subject:** FW: Hot Topics

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Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Finer, Neil](#); [Gantz, Marie](#)  
**Subject:** FW: Hot Topics  
**Date:** Monday, October 28, 2013 1:25:38 PM  
**Attachments:** [BOOST 2 NEJM.pdf](#)

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\*\*\*\*\*

ORIGINAL ARTICLE

## Oxygen Saturation and Outcomes in Preterm Infants

The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups

### ABSTRACT

#### BACKGROUND

The authors and their affiliations are listed in the Appendix. Address reprint requests to Dr. Ben J. Stenson at the Department of Neonatology, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, United Kingdom, or at ben.stenson@luht.scot.nhs.uk.

The clinically appropriate range for oxygen saturation in preterm infants is unknown. Previous studies have shown that infants had reduced rates of retinopathy of prematurity when lower targets of oxygen saturation were used.

#### METHODS

\*Members of the Benefits of Oxygen Saturation Targeting (BOOST) II Collaborative Groups are listed in the Supplementary Appendix, available at NEJM.org.

In three international randomized, controlled trials, we evaluated the effects of targeting an oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, on disability-free survival at 2 years in infants born before 28 weeks' gestation. Halfway through the trials, the oximeter-calibration algorithm was revised. Recruitment was stopped early when an interim analysis showed an increased rate of death at 36 weeks in the group with a lower oxygen saturation. We analyzed pooled data from patients and now report hospital-discharge outcomes.

This article was published on May 5, 2013, at NEJM.org.

N Engl J Med 2013;368:2094-104.

DOI: 10.1056/NEJMoa1302298

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#### RESULTS

A total of 2448 infants were recruited. Among the 1187 infants whose treatment used the revised oximeter-calibration algorithm, the rate of death was significantly higher in the lower-target group than in the higher-target group (23.1% vs. 15.9%; relative risk in the lower-target group, 1.45; 95% confidence interval [CI], 1.15 to 1.84;  $P=0.002$ ). There was heterogeneity for mortality between the original algorithm and the revised algorithm ( $P=0.006$ ) but not for other outcomes. In all 2448 infants, those in the lower-target group for oxygen saturation had a reduced rate of retinopathy of prematurity (10.6% vs. 13.5%; relative risk, 0.79; 95% CI, 0.63 to 1.00;  $P=0.045$ ) and an increased rate of necrotizing enterocolitis (10.4% vs. 8.0%; relative risk, 1.31; 95% CI, 1.02 to 1.68;  $P=0.04$ ). There were no significant between-group differences in rates of other outcomes or adverse events.

#### CONCLUSIONS

Targeting an oxygen saturation below 90% with the use of current oximeters in extremely preterm infants was associated with an increased risk of death. (Funded by the Australian National Health and Medical Research Council and others; BOOST II Current Controlled Trials number, ISRCTN00842661, and Australian New Zealand Clinical Trials Registry numbers, ACTRN12605000055606 and ACTRN12605000253606.)

**T**HE CLINICALLY APPROPRIATE RANGE FOR oxygen saturation in preterm infants is unknown. Trials in the 1950s showed that unrestricted oxygen increased the rate of severe retinopathy of prematurity. However, when oxygen was subsequently restricted, increased mortality was observed.<sup>1</sup> The first Benefits of Oxygen Saturation Targeting (BOOST) trial showed that in preterm infants who were still receiving oxygen at 32 weeks' gestation, targeting a higher oxygen-saturation range prolonged oxygen dependence.<sup>2</sup> Observational studies suggested that higher oxygen-saturation levels may increase rates of retinopathy of prematurity.<sup>3-5</sup>

In five randomized, masked trials with similar protocols conducted in the United States,<sup>6</sup> Australia, New Zealand, Canada, and the United Kingdom<sup>7</sup> involving infants born before 28 weeks' gestation, investigators are evaluating the effects of targeting a range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, on survival and neurodevelopmental outcomes at 18 months to 2 years after the expected delivery date. In all five trials, Masimo Radical pulse oximeters were used to measure oxygen saturation.

During the trials, investigators in the United Kingdom found that standard Masimo Radical oximeters returned fewer oxygen-saturation values in the range of 87 to 90% than expected.<sup>8</sup> We investigated this oximeter finding, because such a discrepancy might affect the study groups differently, and we found that there was a shift up in the oximeter-calibration curve between 87% and 90%. This reduced the frequency of displayed oxygen-saturation values ranging from 87 to 90% and caused values ranging from 87 to 96% to read 1 to 2% higher. Masimo supplied software with a revised calibration algorithm that eliminated the problem and was similar to the calibration of other oximeters.<sup>8</sup>

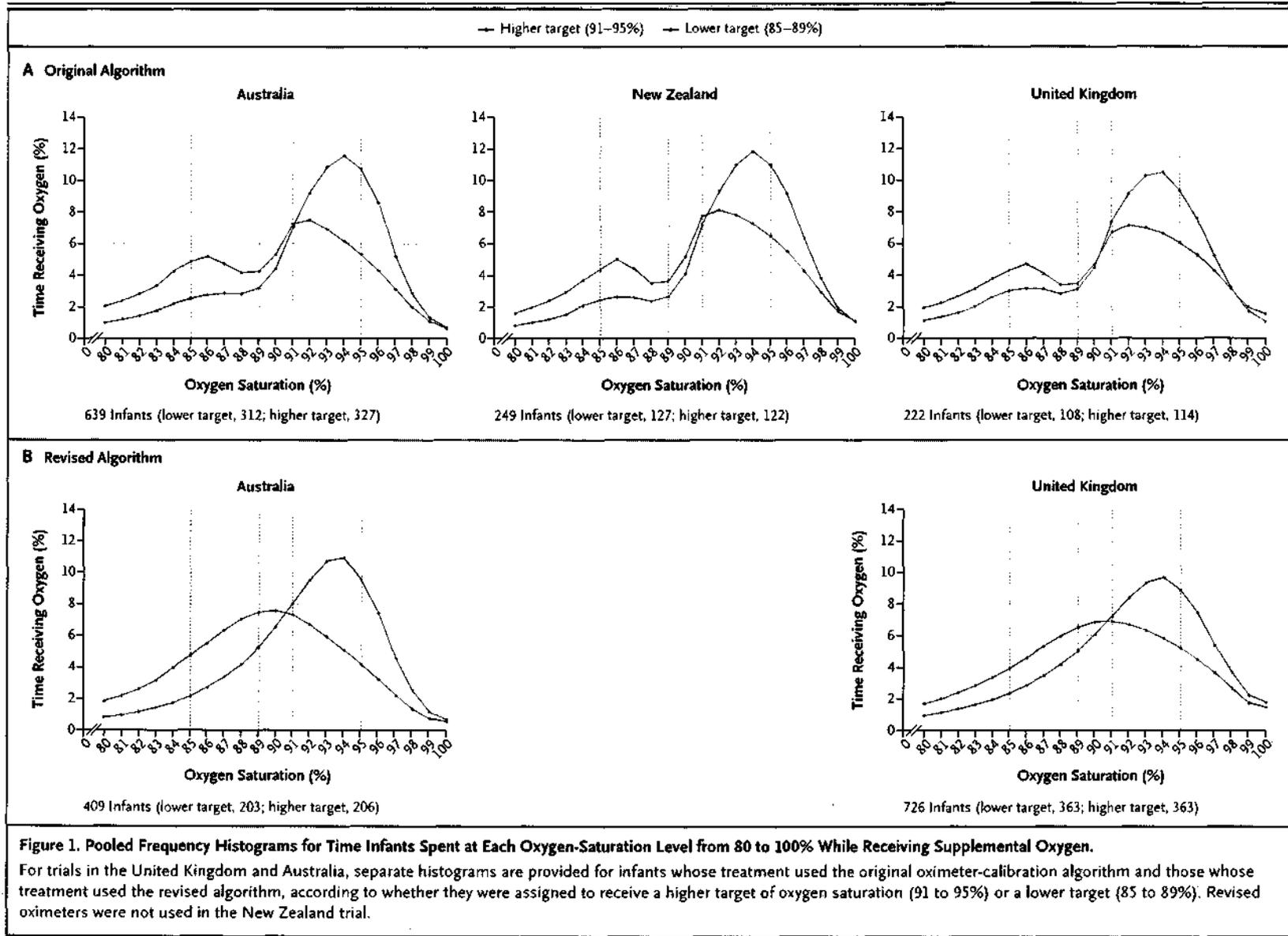
Approximately halfway through the trials, between December 2008 and May 2009, oximeters in the United Kingdom and Australian trials were changed to the new calibration algorithm, and the new algorithm was used for all infants who were subsequently enrolled. The New Zealand trial oximeters were not changed because recruitment had nearly finished. Analysis of oxygen-saturation distributions showed that the revised calibration algorithm improved oxygen-saturation targeting, with clearer separation in oxygen-

saturation patterns between the two study groups and more time in the intended oxygen-saturation range (Fig. 1, and Tables S1.1 through S1.4 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

In 2010, in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT),<sup>6</sup> investigators reported that infants treated with the use of an oxygen-saturation target of 85 to 89%, as compared with a target of 91 to 95%, had decreased rates of retinopathy of prematurity (8.6% vs. 17.9%,  $P < 0.001$ ) but increased rates of death (19.9% vs. 16.2%,  $P = 0.045$ ). At that time, patients were being recruited for the BOOST II trials, and after analyzing data from the original trials, the data and safety monitoring committees did not advise stopping recruitment.<sup>9</sup>

In December 2010, the data and safety monitoring committees in the United Kingdom, Australian, and New Zealand undertook a pooled interim safety analysis,<sup>10</sup> including data from the 2315 infants enrolled in the three BOOST II trials and the 1316 infants enrolled in SUPPORT.<sup>6</sup> The sole outcome that the committees analyzed was survival at 36 weeks' gestation. Guidelines prespecified that the results would not be released to the investigators unless a difference in survival in all infants or in those recruited after the oximeter-calibration changes exceeded 3 SE ( $P < 0.003$ ). In the three trials reported here, mortality at 36 weeks showed heterogeneity between the original oximeter-calibration algorithm and the revised algorithm ( $P = 0.006$  for interaction). Among the 1260 infants for whom the original oximeter algorithm was used, there was no significant between-group difference in mortality. However, in the 1055 infants for whom the revised algorithm was used, infants with an oxygen-saturation target of 85 to 89%, as compared with those with a target of 91 to 95%, had an increased rate of death at 36 weeks (21.8% vs. 13.3%,  $P < 0.001$ ). At that time, recruitment to the present trials in the United Kingdom and Australia was closed.<sup>10</sup> The present New Zealand trial had finished recruiting.

The primary outcome of the Neonatal Oxygenation Prospective Meta-analysis (NeOProm) Collaboration<sup>7</sup> is death or severe neurosensory disability at 18 months to 2 years of age, corrected for prematurity. SUPPORT recently report-



ed no difference in this composite outcome but an increased rate of death at 18 to 22 months in infants in the group with a lower oxygen-saturation target.<sup>11</sup> Because a finding of increased mortality with a lower oxygen-saturation target could have an influence on clinical practice,<sup>10,11</sup> we now report a pooled analysis of individual patient data with respect to outcomes at hospital discharge in the United Kingdom, Australian, and New Zealand BOOST II trials.

## METHODS

### PATIENTS

The planned study sample sizes were 1200 infants each for the United Kingdom and Australian trials and 340 infants for the New Zealand trial. Infants were enrolled from March 1, 2006, until December 24, 2010. Randomization was performed centrally by computer and separately for each trial. In the United Kingdom, a minimization procedure was used to balance study-group assignment according to sex, gestational age, and center. In Australia and New Zealand, randomization was stratified according to sex, gestational age, center, single birth or multiple births, and whether birth took place in the hospital where enrollment took place. Infants were eligible if they had been born within the past 24 hours and before 28 weeks' gestation. Infants were excluded if they were considered to be unlikely to survive, had a major congenital abnormality, or would not be available for follow-up.

The ethics committee at each center approved the study before randomization. All parents provided written informed consent.

### ENROLLMENT AND TREATMENT

Infants were randomly assigned to treatment with the use of an oxygen-saturation target of 85 to 89% (lower-target group) or 91 to 95% (higher-target group). To mask the intervention, the study oximeters were modified internally so that readings of 85 to 95% showed an oxygen saturation that was either 3 percentage points higher or 3 percentage points lower than the actual value. Thus, a displayed reading of 90% corresponded to an actual oxygen saturation of 87% in one group and 93% in the other. To achieve the intended oxygen-saturation range in either group, clinical staff members targeted displayed readings in the range of 88 to 92%. Displayed oxygen-saturation

values gradually reverted to actual values when the measured value was outside the range of 85 to 95%.

Only study oximeters were used from the time of randomization until 36 weeks, unless infants died or were discharged home. If infants were in stable condition while breathing ambient air before 36 weeks, oximetry could be discontinued, but if oximetry resumed before 36 weeks, study oximeters were used. Data regarding oxygen saturation were downloaded and merged with chart data on which staff recorded the inspired oxygen concentration in blocks of either 20 minutes (in the United Kingdom) or 60 minutes (in Australia and New Zealand) to enable assessment of compliance with target ranges.

### ASSESSMENTS

Data were recorded on case-report forms at each center and checked centrally. Retinopathy of prematurity was classified according to the International Classification of Retinopathy of Prematurity<sup>12</sup> and is reported if infants were treated according to the Early Treatment for Retinopathy of Prematurity (ETROP) criteria.<sup>13</sup> Necrotizing enterocolitis was listed if it required surgery or caused death. Oxygen treatment at 36 weeks was recorded in all three trials. In the United Kingdom, bronchopulmonary dysplasia was additionally defined as requiring supplemental oxygen at 36 weeks to maintain an actual oxygen saturation of 90%.

When the oximeter-calibration algorithm was revised, infants continued to be treated with the use of the oximeter-calibration version to which they were originally assigned. Clinical staff members were not informed about the nature of the software revision. No further training about oxygen-saturation targeting was provided.

### STUDY OVERSIGHT

The BOOST II trials were funded and conducted independently, with similar protocols (available at NEJM.org). The Australian trial was funded by the National Health and Medical Research Council, the United Kingdom trial by the Medical Research Council, and the New Zealand trial by the New Zealand Health Research Council. Masimo supplied the oximeters used in the study under lease, but company representatives were not involved in the design of the study, in the analysis of the data, or in the preparation of the manuscript.

### STATISTICAL ANALYSIS

A joint analysis plan prespecified that data from the three trials would be pooled and outcomes reported for all infants and for those who underwent randomization before and after the revision of the oximeter-calibration algorithm.

All analyses were performed with the use of Stata SE 11.2 software (StatCorp). All analyses were performed separately by the trial statisticians in the United Kingdom and Australia and were cross-checked. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance without adjustment for multiple comparisons.

All analyses were performed on the intention-to-treat principle at randomization, regardless of deviations from the protocol. Outcomes were summarized with the use of counts and percentages for categorical variables and of means and standard deviations for normally distributed continuous variables. The magnitude and direction of treatment effects were expressed as relative risks, with 95% confidence intervals adjusted for country. Relative risks were calculated as the event rate in the lower-target group divided by the event rate in the higher-target group. Prespecified subgroup analyses according to the oximeter-calibration algorithm that was used were performed with a statistical test for interaction.

To compare the oxygen-saturation values, the percentage of time spent at each oxygen-saturation value between 60% and 100% was calculated for each infant and pooled for all infants, for time treated with oxygen and for all time evaluated on the oximeter. Offset readings were adjusted back to the actual oxygen-saturation values. We used quadratic interpolation to estimate the distribution of values affected by the transitioning back to actual values of offset readings in which the measured value was outside the range of 85 to 95%. A post hoc survival analysis was performed with the use of cumulative-hazard plots to compare mortality before discharge in the two target groups.

## RESULTS

### PATIENTS

A total of 2448 infants were enrolled in the three trials (973 in the United Kingdom, 1135 in Australia, and 340 in New Zealand). Of these infants, 1261 (51.5%) were treated with the use of

### Figure 2 (facing page). Enrollment and Outcomes.

In the United Kingdom trial, screening of eligible infants was not recorded. Of the infants who underwent randomization, all were included in the analysis except for the following 3: in the United Kingdom trial, 1 infant in the lower-target group for whom consent was not provided and 1 infant in the higher-target group who was found to be ineligible because of age; and in the Australian trial, 1 infant in the lower-target group whose parents withdrew consent. A total of 23 infants (12 in the lower-target group and 11 in the higher-target group) did not receive the intended allocation at all times, mainly because of errors in oximeter allocation that were rectified later. The intervention was discontinued before it was completed in 35 infants, mainly because of parental or clinician wishes or because the infant was transferred to another center that was unable to continue the intervention. When the trials were stopped early after the interim safety analysis, the intervention was stopped in 43 infants in each of the two study groups.

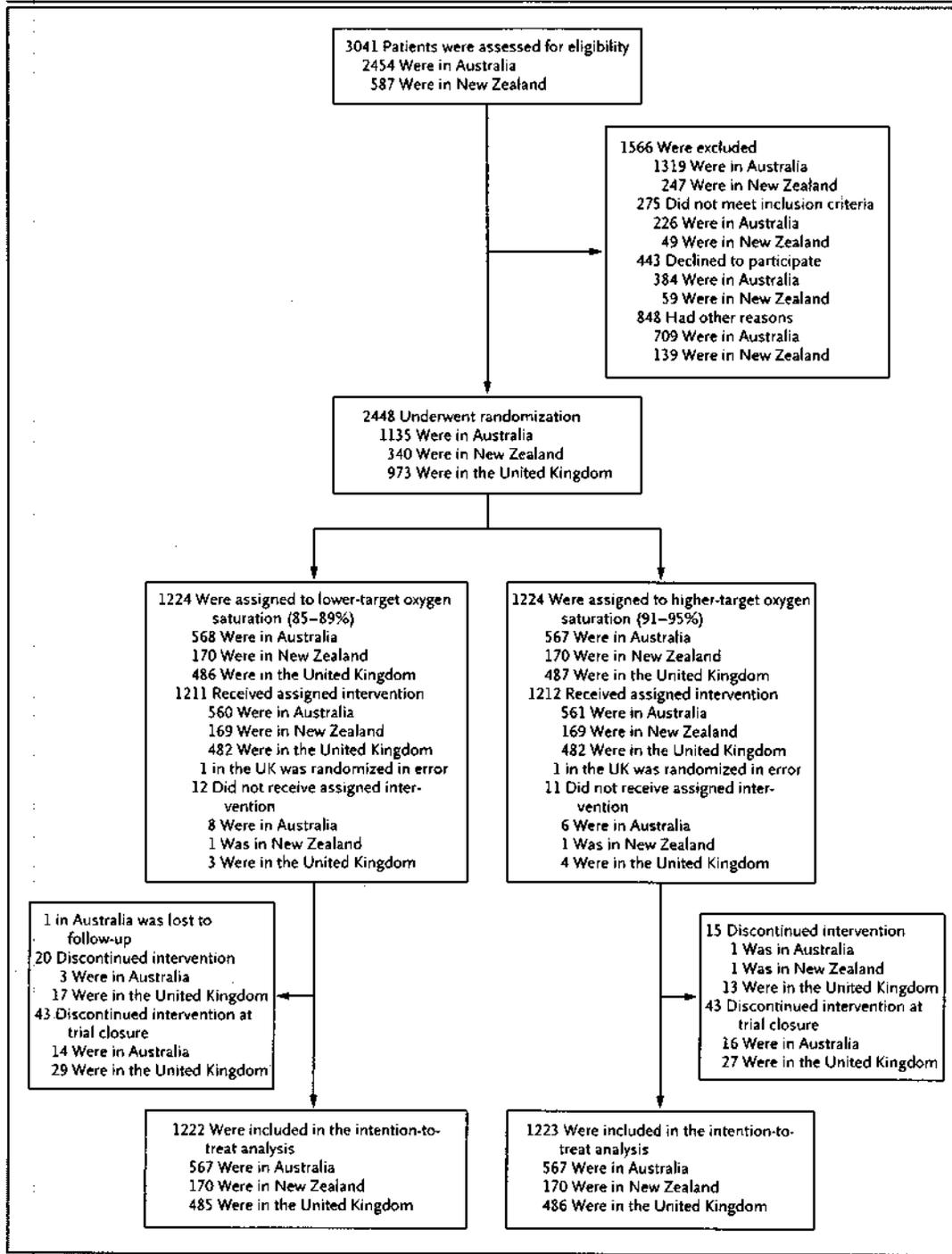
the original oximeter-calibration algorithm and 1187 (48.5%) with the use of the revised algorithm (Fig. 2). Baseline demographic and clinical characteristics were similar in the two target groups, among the three trials, and in the two algorithm groups (Table 1). Forest plots of pooled outcomes at hospital discharge are shown in Figure 3. Outcome data from the individual trials are provided in Tables S2.1 and S2.2 in the Supplementary Appendix.

### RATE OF DEATH

Among the 1187 infants for whom the revised oximeter-calibration algorithm was used, those in the lower-target group had a higher rate of death than those in the higher-target group before hospital discharge (23.1% vs. 15.9%; relative risk in the lower-target group, 1.45; 95% confidence interval [CI], 1.15 to 1.84; *P*=0.002). These findings mean that 14 infants would need to be treated with a higher oxygen-saturation target in order to prevent 1 death. Among the 1261 infants for whom the original oximeter-calibration algorithm was used, there were no significant between-group differences in outcomes at hospital discharge. There was heterogeneity between the rates of death among infants whose treatment used the original oximeter-calibration algorithm, as compared with the revised algorithm (*P*=0.006 for interaction), but not for other outcomes.

In all data combined, there was no significant difference in rate of death in the lower-target

OXYGEN SATURATION AND OUTCOMES IN PRETERM INFANTS



group, as compared with the higher-target group (19.2% vs. 16.6%; relative risk, 1.16, 95% CI, 0.98 to 1.37;  $P=0.09$ ), but infants in the lower-target group had a reduced rate of treatment for retinopathy of prematurity (10.6% vs. 13.5%; relative risk, 0.79; 95% CI, 0.63 to 1.00;  $P=0.045$ )

and an increased rate of necrotizing enterocolitis requiring surgery or causing death (10.4% vs. 8.0%; relative risk, 1.31; 95% CI, 1.02 to 1.68;  $P=0.04$ ). Although significantly fewer infants in the lower-target group were treated with oxygen at 36 weeks in the three trials, there was no

Table 1. Baseline Characteristics of the Infants, According to Trial and Study Group.\*

Characteristic	Australia		New Zealand		United Kingdom		Combined Trials	
	Lower Target (N=568)	Higher Target (N=567)	Lower Target (N=170)	Higher Target (N=170)	Lower Target (N=486)	Higher Target (N=487)	Lower Target (N=1224)	Higher Target (N=1224)
Male sex — no./total no. (%)	293/568 (51.6)	295/566 (52.1)	90/170 (52.9)	90/170 (52.9)	258/486 (53.1)	259/487 (53.2)	641/1224 (52.4)	644/1223 (52.7)
Birth weight — g	817±177	833±190	873±202	884±186	818±182	824±188	826±184	837±189
Gestational age — wk	26.0±1.16	26.0±1.18	26.1±1.23	26.1±1.19	26.0±1.30	26.0±1.31	26.0±1.22	26.0±1.23
Multiple births — no./total no. (%)	138/568 (24.3)	135/567 (23.8)	46/170 (27.1)	46/170 (27.1)	138/485 (28.5)	136/486 (28.0)	322/1223 (26.3)	317/1223 (25.9)
Birth outside enrollment hospital — no./total no. (%)	44/568 (7.7)	42/567 (7.4)	11/170 (6.5)	13/170 (7.6)	57/486 (11.7)	60/487 (12.3)	112/1224 (9.2)	115/1224 (9.4)
Use of antenatal glucocorticoids — no./total no. (%)								
Complete regimen	303/568 (53.3)	320/567 (56.4)	94/170 (55.3)	103/170 (60.6)	306/483 (63.4)	301/484 (62.2)	703/1221 (57.6)	724/1221 (59.3)
Incomplete regimen	198/568 (34.9)	199/567 (35.1)	56/170 (32.9)	49/170 (28.8)	137/483 (28.4)	135/484 (27.9)	391/1221 (32.0)	383/1221 (31.4)
Admission temperature — °C	36.0±1.05	36.1±0.93	36.4±1.01	36.4±0.89	36.6±0.93	36.6±0.94	36.3±1.04	36.3±0.96

\* Plus-minus values are means ±SD. The oxygen-saturation targets were 85 to 89% (lower-target group) or 91 to 95% (higher-target group).

significant between-group difference in the rate of bronchopulmonary dysplasia, as defined physiologically in the United Kingdom trial.

There were more deaths in the lower-target group, but no single cause dominated the difference (Table S3 in the Supplementary Appendix). Figure 4 shows cumulative hazard plots for mortality before discharge, according to which version of the oximeter-calibration algorithm was used. The difference in the proportions of infants surviving in the two groups accumulated gradually after the first week after birth.

**EFFECT OF OXIMETER RECALIBRATION**

Figure 1 summarizes pooled distributions of oxygen saturation during the administration of supplemental oxygen (Fig. S1 and Tables S1.1 through S1.4 in the Supplementary Appendix). With the original oximeter-calibration algorithm, there were fewer oxygen-saturation values between 87% and 90% in the two target groups and little separation between the peaks of the oxygen-saturation distributions. With the revised algorithm, the dip in oxygen-saturation values between 87% and 90% was eliminated, and there was clearer separation between the two target groups.

**PER-PROTOCOL ANALYSIS AND ADVERSE EVENTS**

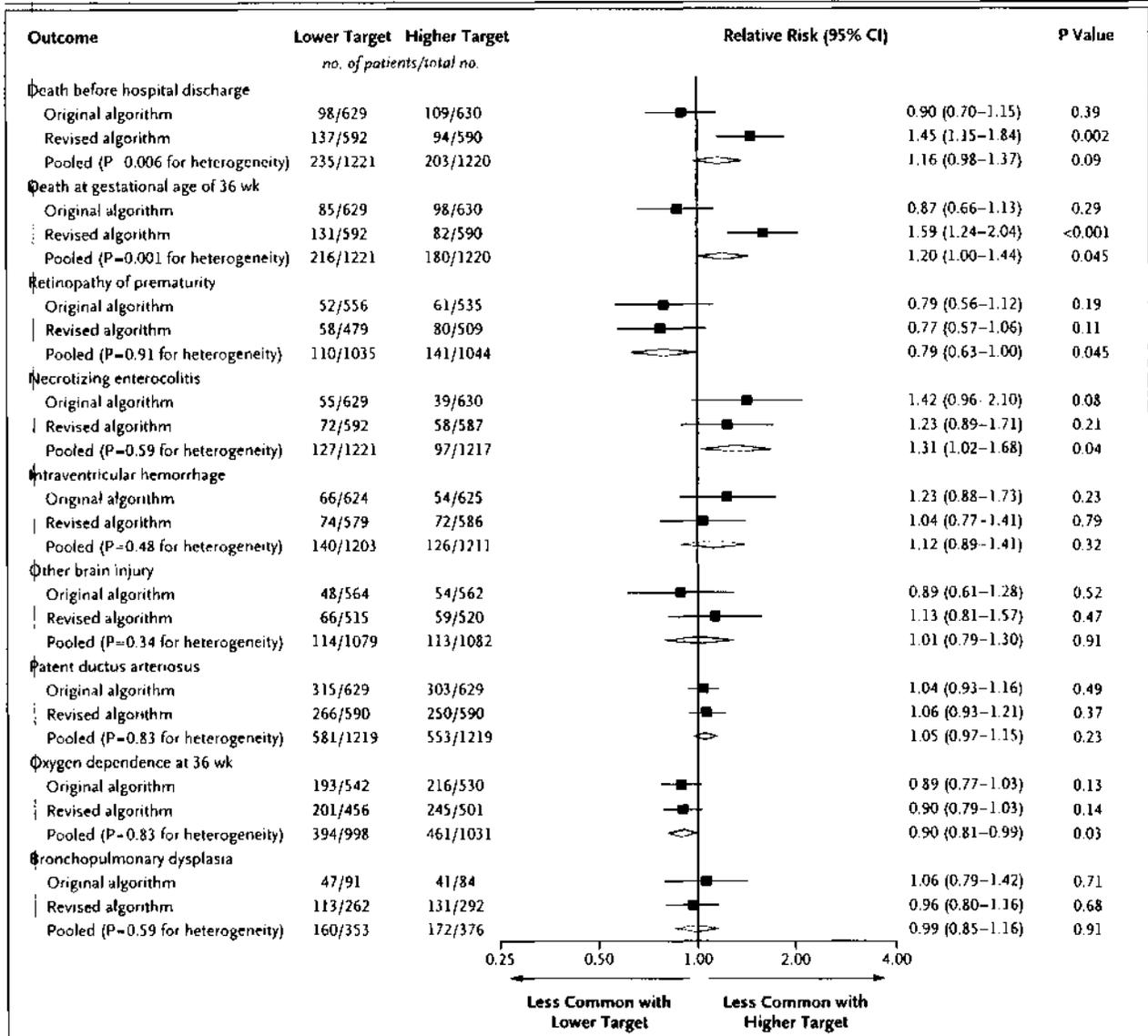
The results of a per-protocol analysis that excluded 23 infants who did not receive the intended intervention were similar to the findings in the intention-to-treat analysis. The few adverse events that were reported are listed in full in Table S4 in the Supplementary Appendix.

**DISCUSSION**

The present trials were closed early when a pooled interim safety analysis showed that infants in the group treated with an oxygen-saturation target of 85 to 89%, as compared with 91 to 95%, had an increased rate of death at 36 weeks.<sup>10</sup> This report includes outcomes for all infants until hospital discharge. A substantial difference in mortality persisted, and other important outcomes were influenced significantly by the targeted oxygen-saturation range.

The between-group difference in the rate of death accrued over many weeks of the intervention and was not attributable to any single cause of death. It is unclear why the rate of death was

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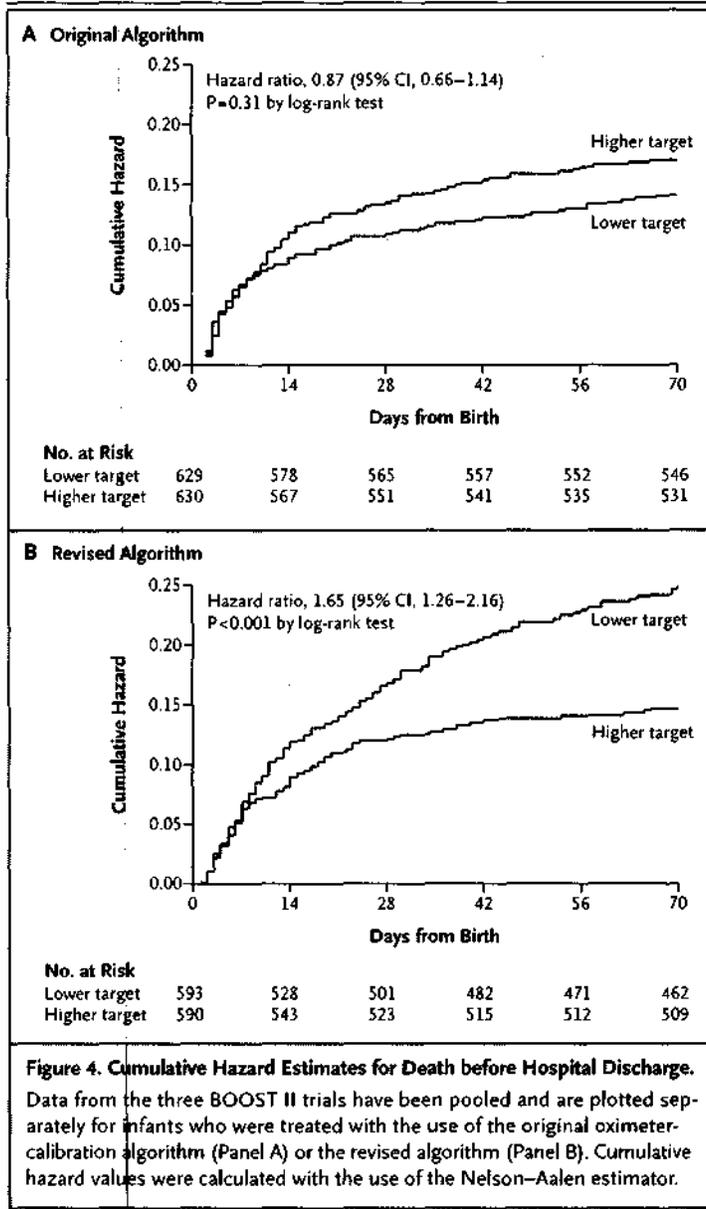


**Figure 3. Combined Discharge Outcomes from the Three Trials, According to Oxygen-Saturation Target and Status of the Oximeter-Calibration Algorithm.**

Shown are discharge outcomes for all infants in the lower-target group for oxygen saturation (85 to 89%) and the higher-target group (91 to 95%) on the basis of whether their treatment involved the original algorithm for oximeter calibration or the revised algorithm. Also shown are P values for heterogeneity for such algorithm use, as calculated with the use of chi-square tests. Oxygen dependence at a gestational age of 36 weeks was measured in all three trials. In the United Kingdom trial, bronchopulmonary dysplasia was additionally defined as requiring supplemental oxygen to maintain an actual oxygen saturation of 90% or more. Intraventricular hemorrhage was defined as only grade III or IV events, and patent ductus arteriosus was defined as a condition requiring medical or surgical treatment. The category of "other brain injury" included porencephaly, ventriculomegaly, posthemorrhagic hydrocephalus requiring a shunt or reservoir, periventricular leukomalacia, and cerebral atrophy. Relative risks and P values were adjusted for country.

higher in the lower-target group than in the higher-target group. Detailed post hoc analysis of the oxygen-saturation patterns of infants who survived and died will be required to further explore this issue. Interpretation of the results is

complicated by the change in oximeter calibration approximately halfway through the trials. This modification rectified an artifact in the original oximeters that appeared to decrease the difference between groups in oxygen-saturation



patterns. The revised Masimo oximeter-calibration algorithm may be more relevant to future clinical practice because it resembles the calibration in other commonly used oximeters; the original calibration algorithm is no longer available.<sup>8</sup>

There was significant heterogeneity in treatment effect between the original oximeter-calibration algorithm and the revised algorithm with respect to mortality but not retinopathy of prematurity or necrotizing enterocolitis. This may

be because each of these outcomes may be influenced at different oxygen saturations. The oxygen-saturation histograms in Figure 1 show that when the oximeter-calibration algorithm was revised, there was no increase in the proportion of time spent with oxygen-saturation values below 85% in the lower-target group. This suggests that the increase in mortality cannot be attributed to an increase in the time spent with very low oxygen-saturation values.

Infants in the lower-target group had a significant decrease in the rate of treatment for retinopathy of prematurity, a finding that is consistent with the results of trials conducted in the 1950s<sup>4</sup> and SUPPORT.<sup>6,11</sup> Because treatment for this condition is usually effective, blindness was rare, with similar rates in the two target groups in SUPPORT.<sup>12</sup> However, retinopathy of prematurity causes other structural and functional eye abnormalities that can be visually disabling,<sup>14</sup> and these may become more common if the reported survival advantage with a higher oxygen saturation influences clinical practice. Treatment for retinopathy of prematurity was more frequent in the two target groups in the United Kingdom than in Australia and New Zealand, suggesting that treatment thresholds may have differed even though the same criteria were used.<sup>15</sup>

In the pooled data, the lower oxygen-saturation target significantly increased the rate of necrotizing enterocolitis requiring surgery or causing death. This definition excludes milder cases of necrotizing enterocolitis with more subjective features. It is plausible that a lower oxygen saturation might influence bowel ischemia.

The increased proportion of infants receiving oxygen at 36 weeks in the higher-target group probably reflects, in part, the increased oxygen needed to achieve the target. As in SUPPORT,<sup>6</sup> when bronchopulmonary dysplasia was defined on the basis of a physiological test in the United Kingdom trial, there was no significant between-group difference in this diagnosis.

With the original oximeters in the present trials, the peak median oxygen-saturation values while infants were receiving supplemental oxygen were approximately 89% in the lower-target group and 92% in the higher-target group, as compared with 91% and 94%, respectively, in SUPPORT.<sup>6</sup> Although the same intended targets

OXYGEN SATURATION AND OUTCOMES IN PRETERM INFANTS

were used, quite different oxygen-saturation patterns were achieved in our studies, as compared with those in SUPPORT. When the oximeter-calibration algorithm was revised, the lower-target groups in the present trials spent more time in the intended range, and mortality in these groups increased. With greater or lesser adherence to the intended range, the effect of oxygen-saturation targets on mortality may vary, so the best estimate of the effect of oxygen saturation on mortality is unknown. Other interventions that influence oxygen targeting may influence mortality and should also be researched carefully.<sup>16</sup>

Monitoring of oxygen saturation has largely replaced the practice of monitoring the arterial partial pressure of oxygen (PaO<sub>2</sub>)<sup>17,18</sup> and has effectively lowered the range of PaO<sub>2</sub> for preterm infants, as compared with previously recommended PaO<sub>2</sub> targets.<sup>19,20</sup> Infants in the lower-target group may have had times when the PaO<sub>2</sub> was below 40 mm Hg.<sup>19</sup> The optimal measure of oxygenation to guide clinical practice is not known.

Without the pooled interim safety analysis,<sup>10</sup> continued recruitment to the present trials might have resulted in potentially avoidable deaths in the lower-target group. Consensus is needed about the roles of data and safety monitoring committees of simultaneous, similar, independent trials in respect to patient safety. The use of an interim analysis carries a statistical risk that, by chance, the observed effect might not represent the true effect that would have been shown if the trial had continued.<sup>21</sup> Thus, the prespecified criteria for unmasking the results of the

interim safety analysis<sup>11</sup> required a difference in survival of 3 SE (99.73% confidence interval).

The clinically appropriate oxygen-saturation range for extremely preterm infants is unknown and may vary with advancing gestational and post-natal age. The present trials and the SUPPORT trial suggest that targeting a range of 91 to 95% is safer than targeting a range of 85 to 89%, but other ranges have not been investigated. The follow-up results from SUPPORT show no significant difference in rates of later disability.<sup>11</sup> The ongoing NeOProm Collaboration<sup>7</sup> will eventually provide follow-up data on approximately 5000 infants and may further inform clinical practice.

In conclusion, preterm infants born before 28 weeks' gestation with a target oxygen saturation of 85 to 89% had a significantly higher rate of death than did those with a target of 91 to 95% in a subgroup whose treatment involved an oximeter-calibration algorithm similar to that in current use.<sup>8</sup> Our findings strongly favor the avoidance of targeting an oxygen saturation of less than 90% among such infants, according to readings on current oximeters.<sup>6,10,11,22</sup>

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the many parents and clinicians who participated in these studies; the late Dr. Edmund Hey, for his contribution to study development; and Masimo for providing the modified calibration algorithms and for technical support.

APPENDIX

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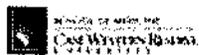
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I noticed I sent Tait just a portion of the questions so I resent them and he approved. Just wanted to make sure you have this for your record since I'm sure others may ask these questions and now have them at our fingertips.

Thanks, as always, for your excellent input!

Best,  
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**Sent:** Friday, October 25, 2013 10:23 AM  
**To:** Myles, Renate (NIH/OD) [E]; Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

ok

---

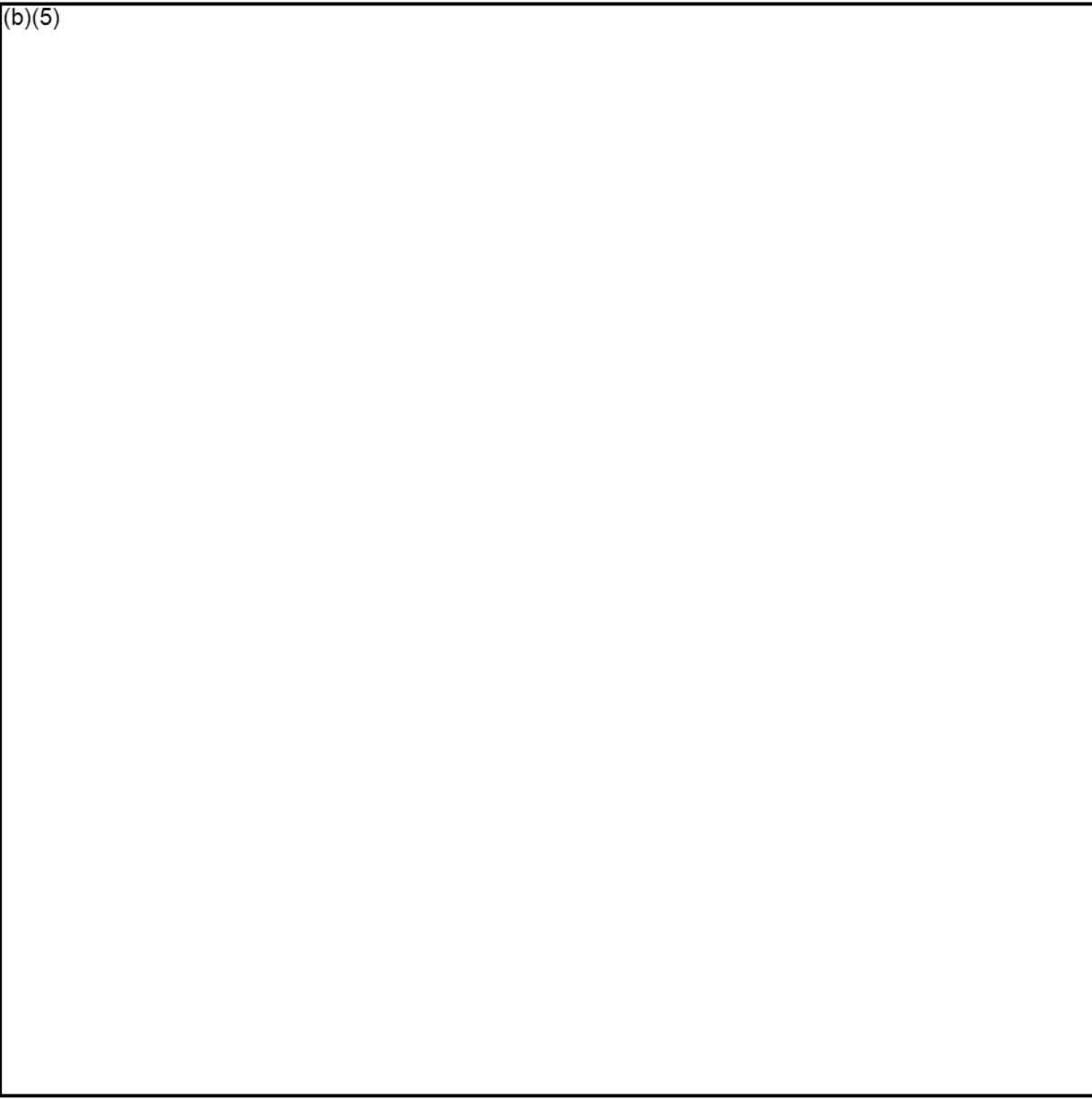
**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Friday, October 25, 2013 10:20 AM  
**To:** Sye, Tait (OS/ASPA); Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

Hi Tait:

Sorry, but I just noticed that I hadn't included all of the QA (and included duplicates instead). Not sure what happened there. Below is the full set. Take a look and let me know if you have any concerns. It's pretty standard stuff.

Thanks,  
Renate

(b)(5)



(b)(5)

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, October 25, 2013 9:12 AM  
**To:** Sye, Tait (OS/ASPA); Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

Hi Tait:

Is this okay to provide to Kim? She's been waiting a few days since folks have been catching up from shutdown.

Thanks,  
Renate

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 5:10 PM  
**To:** Sye, Tait (OS/ASPA); Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

No, nothing yet. At the start, Kim said they may hold it until there is a decision by HHS on the outcome of the meeting, but nothing definitive. When I send her the responses, I'll ask again.

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**From:** Sye, Tait (OS/ASPA)  
**Sent:** Thursday, October 24, 2013 5:09 PM  
**To:** Myles, Renate (NIH/OD) [E]; Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

Hi Renate-

Any update on when the segment will air?

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Thursday, October 24, 2013 5:04 PM  
**To:** Sye, Tait (OS/ASPA); Dreyfuss, Ira (HHS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

ADD

Kim Skeen had additional questions  
Deadline: today

**Were reports generated from these interim data checks? Please provide copies of these reports.**

(b)(5)

**How many interim data checks were done during the SUPPORT study? What were the results?**

(b)(5)

**Were reports generated from these interim data checks? Please provide copies of these reports.**

(b)(5)

**Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?**

(b)(5)

**During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?**

(b)(5)

**From:** Sye, Tait (OS/ASPA)  
**Sent:** Monday, September 09, 2013 9:15 PM  
**To:** Myles, Renate (NIH/OD) [E]; Dreyfuss, Ira (HHS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush,

Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

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**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

Hi Ira:

See change highlighted in yellow below.

Thanks,

Renate

---

**From:** Dreyfuss, Ira (HHS/ASPA)

**Sent:** Monday, September 09, 2013 8:03 PM

**To:** Myles, Renate (NIH/OD) [E]; Sye, Tait (OS/ASPA); HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)

**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

**Subject:** Re: Interview request: SUPPORT Study (Deadline: immediate)

Ok

Ira

---

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**Sent:** Monday, September 09, 2013 06:47 PM

**To:** Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)

**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ) <ODOCPLInterviews@mail.nih.gov>; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

ADD

Kim Skeen had additional questions:

Deadline: tomorrow

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

(b)(5)

(b)(5)

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

(b)(5)

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

(b)(5)

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**From:** Sye, Tait (OS/ASPA)  
**Sent:** Friday, September 06, 2013 9:29 AM  
**To:** Myles, Renate (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

ok

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**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Friday, September 06, 2013 9:27 AM  
**To:** Sye, Tait (OS/ASPA); OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)  
**Importance:** High

ADD

Kim Skeen  
CBS Sunday Morning  
**Deadline: immediate**

Kim had follow up questions. NIH responses are below:

1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press

reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.

(b)(5)

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

(b)(5)

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

(b)(5)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 11:23 AM  
**To:** Sye, Tait (OS/ASPA); Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** RE: Interview request: (insert subject of interview only)

Yes and Yes.

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**From:** Sye, Tait (OS/ASPA)  
**Sent:** Thursday, August 29, 2013 11:22 AM  
**To:** Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** RE: Interview request: (insert subject of interview only)

Who would do interview? Dr. Guttmacher?

Ok, so long as he sticks to TPs.

**Talking Points:**

(b)(5)

**Hot Button QA:**

(b)(5)

---

**From:** Fine, Amanda (NIH/OD) [E] [<mailto:amanda.fine@nih.gov>]  
**Sent:** Thursday, August 29, 2013 11:20 AM  
**To:** OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** RE: Interview request: (insert subject of interview only)

ADD  
Arthur Allen (Freelancer)  
Science

SUPPORT TRIAL  
[arthurallenw@aol.com](mailto:arthurallenw@aol.com)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 12:23 PM  
**To:** Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Fritz, Craig (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** Interview request: (insert subject of interview only)

Producer: Kim Skeen, for Sharyl Attkison (reporter)  
Organization: CBS Sunday morning  
Phone: 202-457-4383  
Subject: SUPPORT Trial  
Deadline: Today  
Spokesperson: Alan E. Guttmacher, M.D., Director, NICHD  
Expected place of publication: CBS Sunday morning  
Expected date of publication/airing: Sunday, September 1  
Expected prominence: news feature

Skeen called and asked if Dr. Guttmacher would be available for a taping next week, to discuss the NIH's views on the SUPPORT trial ruling. The feeling at our institute is that NIH's view was well represented in the NEJM Perspectives piece last June, and that there really isn't anything new to add. If he is able to find time for a taping, Dr. Guttmacher would reiterate the points made in the Perspectives article.

## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Thursday, May 29, 2014 4:50 PM  
**To:** Blansfield, Earl (NIH/NICHD) [E]  
**Subject:** FW: Interview request: SUPPORT Study (Deadline: today)

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)



**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, October 25, 2013 9:53 AM  
**To:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Akinso, Woleola (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: Interview request: SUPPORT Study (Deadline: today)

Hi all:

This has been cleared.

Bob: I'll send the response to Kim.

Thanks,  
Renate

**From:** Sye, Tait (OS/ASPA)  
**Sent:** Friday, October 25, 2013 9:13 AM  
**To:** Myles, Renate (NIH/OD) [E]; Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

ok

---

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Hi Tait:

Is this okay to provide to Kim? She's been waiting a few days since folks have been catching up from shutdown.

Thanks,  
Renate

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**Sent:** Thursday, October 24, 2013 5:10 PM  
**To:** Sye, Tait (OS/ASPA); Baldauf, Sarah (OS/ASPA)  
**Subject:** RE: Interview request: SUPPORT Study (Deadline: today)

No, nothing yet. At the start, Kim said they may hold it until there is a decision by HHS on the outcome of the meeting, but nothing definitive. When I send her the responses, I'll ask again.

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Hi Renate-

Any update on when the segment will air?

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ADD

Kim Skeen had additional questions  
Deadline: today

***Were reports generated from these interim data checks? Please provide copies of these reports.***

(b)(5)

***How many interim data checks were done during the SUPPORT study? What were the results?***

(b)(5)

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(b)(5)

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**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

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Hi Ira:

See change highlighted in yellow below.

Thanks,  
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Ok

Ira

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**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

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Deadline: tomorrow

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(b)(5)

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(b)(5)

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(b)(5)

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OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Gianelli, Diane M (OASH); Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]

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**Subject:** RE: Interview request: SUPPORT Study (Deadline: immediate)

**Importance:** High

ADD

Kim Skeen

CBS Sunday Morning

**Deadline: immediate**

Kim had follow up questions. NIH responses are below:

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

(b)(5)

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

(b)(5)

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(b)(5)

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**Sent:** Thursday, August 29, 2013 11:23 AM

**To:** Sye, Tait (OS/ASPA); Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)

**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie

(NIH/NICHD) [E]

**Subject:** RE: Interview request: (insert subject of interview only)

Yes and Yes.

**From:** Sye, Tait (OS/ASPA)

**Sent:** Thursday, August 29, 2013 11:22 AM

**To:** Fine, Amanda (NIH/OD) [E]; HHS/OS Interviews; Daniels, Carla (HHS/ASPA/News Division)

**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]

**Subject:** RE: Interview request: (insert subject of interview only)

Who would do interview? Dr. Guttmacher?

Ok, so long as he sticks to TPs.

**Talking Points:**

(b)(5)

**Hot Button QA:**

(b)(5)

**From:** Fine, Amanda (NIH/OD) [E] [<mailto:amanda.fine@nih.gov>]

**Sent:** Thursday, August 29, 2013 11:20 AM

**To:** OS - Interviews; Daniels, Carla (HHS/ASPA/News Division)

**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri

(NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]

**Subject:** RE: Interview request: (insert subject of interview only)

ADD

Arthur Allen (Freelancer)

Science

SUPPORT TRIAL

[arthurallenw@apl.com](mailto:arthurallenw@apl.com)

---

**From:** Bock, Robert (NIH/NICHD) [E]

**Sent:** Wednesday, August 21, 2013 12:23 PM

**To:** Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; ODOCPL Interviews (NIH/OD OCPL ); Fritz, Craig (NIH/OD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]

**Subject:** Interview request: (insert subject of interview only)

Producer: Kim Skeen, for Sharyl Attkison (reporter)

Organization: CBS Sunday morning

Phone: 202-457-4383

Subject: SUPPORT Trial

Deadline: Today

Spokesperson: Alan E. Guttmacher, M.D., Director, NICHD

Expected place of publication: CBS Sunday morning

Expected date of publication/airing: Sunday, September 1

Expected prominence: news feature

Skeen called and asked if Dr. Guttmacher would be available for a taping next week, to discuss the NIH's views on the SUPPORT trial ruling. The feeling at our institute is that NIH's view was well represented in the NEJM Perspectives piece last June, and that there really isn't anything new to add. If he is able to find time for a taping, Dr. Guttmacher would reiterate the points made in the Perspectives article.

**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Tampa Bay Times article related to SUPPORT  
**Date:** Friday, October 25, 2013 9:52:40 AM

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Hi Rose, you've probably already seen this article...

## The parental consent dilemma: Saving extremely premature babies by signing forms

*By Kelley Benham*

*Tampa Bay Times*

October 18, 2013

Our baby was dying a half-dozen ways. She was born in the 23rd week of pregnancy weighing 1 pound, 4 ounces. Twiggy and translucent, her body heaved along with the mechanical whooshing of a ventilator that kept her alive while battering her lungs. No matter what the doctors did, she would probably end up dead or broken.

In the 196 days we sat by her bedside at All Children's Hospital, we signed consent forms allowing nurses to shove tubes down her throat and slip IVs into her thready veins. We consented to central lines that carry an overwhelming infection risk. We consented to chest tubes, blood transfusions and an operation so risky the surgeon fully expected it to kill her.

Signing those forms was my first official act as her mother, and the responsibility made my cheeks hot. But I didn't read a single one. The only thing I remember about any of those forms was how it felt to write next to my name that I was her mom.

Now the medical community is engaged in a furious debate about consent forms used in important pediatric research. Major studies conducted on babies like mine have come under attack from the consumer advocacy group Public Citizen, which says the research put babies at risk, and that parents were not adequately warned.

The debate has ensnared dozens of research institutions and just about every notable pediatric bioethicist in a fundamental debate over how to conduct research on the most vulnerable people on the planet. The government issued a scolding, the researchers and their supporters lashed back, and the critics are calling for review and derailment of current and future research.

This summer as I listened to hours of debate in which very smart people evoked Tuskegee and asked "How many babies must die?" it occurred to me that in all the bluster an essential truth was being lost.

All babies born so young are experiments. The rest is just paperwork.

...

At issue is a study performed on 1,300 extremely premature infants at 23 institutions from 2004 to 2009. Called the SUPPORT study, it was funded by the National Institutes of Health and approved by review boards at every participating institution. This was not the study of some radical treatment. Instead, it looked at already common treatments and asked which worked better. The implications are broad, because the Affordable Care Act mandates this sort of approach. Without it, treatment choices are more

open to influence by gut, insurance payouts and lobbyists.

Doctors know that babies born with underdeveloped lungs need oxygen support to survive. But too much oxygen can wreck developing retinas and make babies blind. As doctors and nurses turn up the oxygen dial on a ventilator to help a struggling baby, they wonder if they are causing eye damage. As they dial it down and allow the baby to work harder to breathe, they wonder if they are damaging lungs or brains. So how much oxygen is the right amount?

Years of practice led to a consensus that a baby's blood oxygen level should be kept between 85 and 95 percent. Alarms sound if those targets are breached. For 6½ months, I sat by my baby's incubator and listened to those alarms, which became more urgent as my daughter struggled. I still hear them sometimes in my sleep.

When the study was designed, no one knew whether 85 percent was better than 95 percent, or where to find sweet spot in between. So researchers randomly sorted the babies into a low-oxygen group with a target of 85-89 percent or a high-oxygen group with a target of 91-95 percent. In a move that enraged critics, researchers rigged the monitors so doctors and nurses couldn't know which group each baby was in. Everyone thought they were aiming for the middle. If a baby was in the low oxygen group, for example, the oxygen saturation would read several points higher on the monitor. All babies stayed within the range commonly accepted as safe.

Critics say it's bad for babies when their care is determined by research protocol, not the judgment of an individual doctor. They say that babies were undoubtedly harmed and that parents should have been warned on consent forms that babies in the low-oxygen group had a greater risk of dying.

But that argument makes a number of assumptions. The first is that researchers expected more babies in the low oxygen group to die, a claim they vigorously dispute. In fact, they say, clinical practice at the time trended toward lower oxygen, because the best evidence said it improved babies' vision without adverse effects. And all the eligible babies were at high risk of death or disability no matter what.

The second is that babies have a single Marcus Welby-type doctor who is certain of what he or she is doing. In reality, critically sick babies are cared for by a constantly rotating team of doctors, nurses, nurse practitioners, residents and specialists. Some are plain smarter or more experienced than others. Some know the baby better than others. Some treat aggressively and some don't. One doctor is pro-life. One has disabled kids. One was unexpectedly widowed. All of these factors influence how they talk to parents, how they assess quality of life and how they interpret risk.

For months I obsessed over my baby's oxygen saturation. The alarms would sound many times in an hour as our daughter struggled and recovered. She didn't hover inside the targeted range ordered by her physicians. She cascaded wildly. Gunk in a tube or even a loud noise or a song she didn't like on the radio would send her crashing. Sometimes all it took to bring her back was another round of the Hokey Pokey. "Keep singing!" our nurse would say. Other times I watched those numbers drop into the 20s as nurses lunged to revive her. Everyone who entered her room had a different threshold for when to intervene. Sometimes a doctor would turn the oxygen up, and as soon as they were gone, the nurse would turn it back down. All this came rushing back to me as I listened to the researchers talk about the "standard of care" as if it were something tangible and logical.

One day, while our baby was still small, one of our favorite doctors explained why it's so hard to know when to fiddle with the oxygen dial. He quoted off the top of his head from the recently completed SUPPORT study, the same study now under attack. He wondered aloud how many babies might go blind so one could live.

"I think about it every day and make my best guess," Dr. Rajan Wadhawan said. "If you're an exact person and a mathematician, it will drive you crazy."

It comforted me, though, to hear him quote that study. It made me feel like he brought more to it than his best guess. He brought an army.

"I stand on the shoulders of giants who came before me," he said.

I knew that before there were any studies, many babies died and were blinded by doctors making their best guesses. I asked Dr. Raj, as we called him, if he ever wondered if he was doing more harm than good. "Every day," he said.

I asked several more doctors the same question. They all gave the same answer.

...

Smart people disagree about whether the SUPPORT study was ethical or safe. It turns out that a few more babies in the low-oxygen group died, and a few more babies in the high-oxygen group developed short-term eye disease. But no matter how you measure it, babies in the study did better than babies not in the study. They had lower rates of blindness, disability and death. As a result of the study, doctors changed the way they treat very premature babies.

Our baby's doctors, while applying their best judgment and their very individual experiences, had broad shoulders to stand on. At other moments in our daughter's care, they had little data to guide them. One doctor made a gutsy call to send our daughter to surgery based on faith and a look on our baby's face. We listened to doctors debate "What's the dose of this drug for a two-pound baby?" and no one was sure, because there was no study to consult. Our baby had to go first.

My daughter is 2 now, entirely healthy, saved from death, disability and blindness by a legion of doctors and nurses at All Children's Hospital to whom I owe a limitless debt. Had I been asked, I probably would have signed her up for a research study. If things had gone well, I might have believed the study had helped. If things had gone poorly, I might have blamed the study and feared I'd been duped. "Informed consent" is a holy grail in pediatric medicine, but I doubt it even exists. Someone would have approached me with another form. If it were a doctor who made eye contact or had a nice smile, I would have signed it.

I would not have read the form, because I did not read any of the forms, because the forms are for lawyers, not for parents. I had not slept in days. I was scared out of my mind. I had the mental capacity of a drunk being chased by bears. What kind of form can protect a parent in a situation like that?

In the time we lived in the NICU, we learned to accept risk. Just to enter that place is to embrace terror and uncertainty. There may be risk to participating in a study, but there is also risk to not participating. I don't believe that ethicists and doctors at two dozen institutions conspired to hurt babies. If they decide to tweak the language in their paperwork, so be it. But second-guessing and finger wagging should not hamstring further studies. At the frontier of human possibility, no form can make medicine a safe or predictable endeavor.

What protects our children most is solid research, and the wisdom drawn from babies who came before.

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 24, 2013 4:31 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Sehr gut. Happy to clarify your request for clarification.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 4:30 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Great, thanks for the clarification. And yes, the yellow highlight is the part I'm asking about.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 24, 2013 4:29 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

You're asking me about what's highlighted in yellow, right? I'm saying that if that's what you're asking me about, it's good.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 4:28 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Sorry, not sure if you're saying it's okay or if you're checking. ☺

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 24, 2013 4:09 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Missed that. Sorry. The yellow highlight? Yes, sure.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 4:08 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Hi Bob:

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance. Just checking in; are you all okay with this clarification?

Renate

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 10:43 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: Additional SUPPORT study questions  
**Importance:** High

See Kathy's note below. Is this change okay? I think that's what is meant, right?

***Were reports generated from these interim data checks? Please provide copies of these reports.***

(b)(5)

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

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Thursday, October 24, 2013 10:18 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Devaney, Stephanie (NIH/OD) [E]  
**Subject:** Re: Additional SUPPORT study questions

This is fine but I worry about (b)(5)

(b)(5)

Kathy Hudson, Ph.D.  
Deputy Director for Science, Outreach, and Policy NIH  
301 496 1455  
kathy.hudson@nih.gov

> On Oct 23, 2013, at 8:18 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

>

> (b)(5)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, October 23, 2013 4:38 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** Revised SUPPORT response

Please see revisions below, per your earlier note.

***Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?***

(b)(5)

***How many interim data checks were done during the SUPPORT study? What were the results?***

(b)(5)

***Were reports generated from these interim data checks? Please provide copies of these reports.***

(b)(5)

***Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?***

(b)(5)

***During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?***

(b)(5)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 4:34 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Hi Renate. Per your request below, here are our responses to the latest round of questions from Kim Skeen.

Bob

***Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?***

(b)(5)

***How many interim data checks were done during the SUPPORT study? What were the results?***

(b)(5)

***Were reports generated from these interim data checks? Please provide copies of these reports.***

(b)(5)

***Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?***

(b)(5)

***During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?***

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, October 21, 2013 2:53 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,  
Renate

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
- Were reports generated from these interim data checks? Please provide copies of these reports.
- Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION  
**Date:** Tuesday, October 22, 2013 1:24:14 PM

---

Agreed.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
rajut@mail.nih.gov

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

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 1:10 PM  
**To:** Spong, Catherine (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

Like Cathy's KISS – one simple suggestion in wording attached

Mona

Mona Jaffe Rowe, M.C.P.

Associate Director for Science Policy,

Analysis and Communication

Eunice Kennedy Shriver National Institute of

Child Health and Human Development

National Institutes of Health, DHHS

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Bethesda, MD 20892-2425

Phone: 301.496.1877/Fax: 301.496.0588

Email: rowem@mail.nih.gov <mailto:rowem@mail.nih.gov>

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:09 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTAL SUPPORT DRAFT INFORMATION  
**Attachments:** Explain the role of the SUPPORT study Data Safety Committee\_cys.docx

My suggestions in track changes

Suggest (b)(5)

**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTAL SUPPORT DRAFT INFORMATION

I think (b)(5)

My own take is just to say:

(b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:43 AM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** CONFIDENTAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??

Let me know

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

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301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

From: Childress, Kerri (NIH/NICHD) [E]  
Sent: Monday, October 21, 2013 3:25 PM  
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
Subject: RE: Additional SUPPORT study questions  
Importance: High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

From: Myles, Renate (NIH/OD) [E]  
Sent: Monday, October 21, 2013 2:53 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]

**Subject: FW: Additional SUPPORT study questions**

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]

Sent: Monday, October 21, 2013 12:45 PM

To: Myles, Renate (NIH/OD) [E]

Subject: Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
- Were reports generated from these interim data checks? Please provide copies of these reports.
- Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

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skeenk@cbsnews.com

Page 0452 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Page 0453 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Thursday, May 29, 2014 4:47 PM  
**To:** Blansfield, Earl (NIH/NICHD) [E]  
**Subject:** FW: CONFIDENTAL SUPPORT DRAFT INFORMATION

Per case 42456

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
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Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)



---

**From:** Willinger, Marian (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:05 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTAL SUPPORT DRAFT INFORMATION

Tonse.

This may be semantics but I don't think that (b)(5)

(b)(5)

(b)(5)

I think what is (b)(5)

(b)(5)

Marian

---

**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTAL SUPPORT DRAFT INFORMATION

I think (b)(5)

My own take is just to say:

(b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, October 22, 2013 10:43 AM  
To: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
Subject: CONFIDENTIAL SUPPORT DRAFT INFORMATION

See attached -- perhaps a phone conference would help??  
Let me know

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

From: Childress, Kerri (NIH/NICHD) [E]  
Sent: Monday, October 21, 2013 3:25 PM  
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
Subject: RE: Additional SUPPORT study questions  
Importance: High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

From: Myles, Renate (NIH/OD) [E]  
Sent: Monday, October 21, 2013 2:53 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
Subject: FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to

(b)(5)

(b)(5)

Thanks,

Renate

From: Skeen, Kim [mailto:[SkeenK@cbsnews.com](mailto:SkeenK@cbsnews.com)]  
Sent: Monday, October 21, 2013 12:45 PM

To: Myles, Renate (NIH/OD) [E]

Subject: Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
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- Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

skeenk@cbsnews.com

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Thursday, May 29, 2014 4:52 PM  
**To:** Blansfield, Earl (NIH/NICHD) [E]  
**Subject:** FW: CONFIDENTAL SUPPORT DRAFT INFORMATION

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)



**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:49 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTAL SUPPORT DRAFT INFORMATION

Not sure, but might (b)(5)

(b)(5)

Alan

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:43 AM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** CONFIDENTAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??  
Let me know

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
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**Sent:** Monday, October 21, 2013 3:25 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions  
**Importance:** High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

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**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,  
Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

- How many interim data checks were done during the SUPPORT study? What were the results?
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Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeen@cbsnews.com](mailto:skeen@cbsnews.com)

## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Thursday, May 29, 2014 4:51 PM  
**To:** Blansfield, Earl (NIH/NICHD) [E]  
**Subject:** FW: CONFIDENTIAL SUPPORT DRAFT INFORMATION  
**Attachments:** Explain the role of the SUPPORT study Data Safety Committee.docx

### *Mona*

Mona Jalife Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
Building 31, Rm 2A-18  
31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)



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**Subject:** CONFIDENTIAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??  
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Rosemary D. Higgins, MD  
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**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions  
**Importance:** High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, October 21, 2013 2:53 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,  
Renate

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

Renate,

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Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

- ***Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?***

(b)(5)

- ***How many interim data checks were done during the SUPPORT study? What were the results?***

(b)(5)

- ***Were reports generated from these interim data checks? Please provide copies of these reports.***

(b)(5)

- ***Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?***

(b)(5)

- ***During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?***

(b)(5)

Page 0465 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

**From:** Spong, Catherine (NIH/NICHD) [E]  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]  
**Subject:** RE: Another item in the Tampa Bay newspaper  
**Date:** Tuesday, October 22, 2013 8:50:46 AM

---

Very impressive article, she really understands the issues and delivered the message powerfully  
I hope many people read the Tampa Bay newspaper  
Can we get other papers to run the story?

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 8:43 AM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** RE: Another item in the Tampa Bay newspaper

Would it be okay for me to send her a fan email?

Alan

Alan E. Guttmacher, M.D.  
Director  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
National Institutes of Health  
31 Center Drive  
Building 31, Room 2A03  
Bethesda, MD 20892-2425  
  
Phone: 301-496-3454  
e-mail: [guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)  
url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Childress, Kerri (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 8:29 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** RE: Another item in the Tampa Bay newspaper

Very powerful. Kerri

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 8:13 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** Another item in the Tampa Bay newspaper

<http://www.tampabay.com/news/perspective/saving-babies-by-signing-forms/2147897>

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Willinger, Marian (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 4:43:55 PM

---

Thanks- this is getting out of hand.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 4:38 PM  
**To:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

FYI

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

**From:** "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>  
**Date:** October 21, 2013, 4:37:05 PM EDT  
**To:** "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>  
**Cc:** "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Burklow, John (NIH/OD) [E]" <BurklowJ@OD.NIH.GOV>, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>, "Fine, Amanda (NIH/OD) [E]" <amanda.fine@nih.gov>  
**Subject:** Re: Additional SUPPORT study questions

Hi all - best to have (b)(5) hopefully she can use some of the materials we used before. Don't think we can (b)(5)

(b)(5)

On Oct 21, 2013, at 3:45 PM, "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov> wrote:

Wonderful, thank you Renate. Kerri

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, October 21, 2013 3:45 PM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Yes, definitely. They've been working on this for months now and their note is always "we need it today". Plus, they're a Sunday show. I'll let her know we'll get her responses tomorrow.

---

**From:** Childress, Kerri (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:44 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

Renate: Please see Dr. Higgins' response below. Can this wait till tomorrow? I know reporters always make it sound urgent, but she's been working on this story for more than a month now. Your call how you think we should handle this.

Kerri

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:38 PM  
**To:** Childress, Kerri (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** Re: Additional SUPPORT study questions

I am at NICHD T32 conference and am speaking shortly- can this wait until tomorrow am? Otherwise I can do after 5 pm

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 3:24 PM, "Childress, Kerri (NIH/NICHD) [E]" <[kerri.childress@nih.gov](mailto:kerri.childress@nih.gov)> wrote:

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

---

**From:** Myles, Renate (NIH/OD) [E]  
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**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

Thanks,

Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]

**Sent:** Monday, October 21, 2013 12:45 PM

**To:** Myles, Renate (NIH/OD) [E]

**Subject:** Additional SUPPORT study questions

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Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Willinger, Marian (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 4:19:35 PM

---

Ok- let's talk tomorrow

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 4:15 PM  
**To:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Re: Additional SUPPORT study questions

Still in the meeting and scheduled to talk soon- I can talk to you at 5 or tomorrow

I don't need to respond until tomorrow

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 3:48 PM, "Willinger, Marian (NIH/NICHD) [E]" <willingm@exchange.nih.gov> wrote:

Can you give me a call?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:32 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

I need some advice here- at each point the (b)(5)

How do we respond and should (b)(5) be involved? Both Alan and I have talked to the CBS reporters and there have been many questions answered via email

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

**From:** "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>  
**Date:** October 21, 2013, 3:24:38 PM EDT  
**To:** "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Cc:** "Fine, Amanda (NIH/OD) [E]" <amanda.fine@nih.gov>, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>  
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Thank you so very much, Kerri

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**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,  
Renate

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- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim  
Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 3:48:40 PM

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301-435-6896

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:32 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

I need some advice here- at each point the (b)(5) [redacted]  
How do we respond and should (b)(5) [redacted] be involved? Both Alan and I have talked to the CBS reporters and there have been many questions answered via email

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

**From:** "Childress, Kerri (NIH/NICHD) [E]" <[kerri.childress@nih.gov](mailto:kerri.childress@nih.gov)>  
**Date:** October 21, 2013, 3:24:38 PM EDT  
**To:** "Bock, Robert (NIH/NICHD) [E]" <[bockr@exchange.nih.gov](mailto:bockr@exchange.nih.gov)>, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**Cc:** "Fine, Amanda (NIH/OD) [E]" <[amanda.fine@nih.gov](mailto:amanda.fine@nih.gov)>, "Rowe, Mona (NIH/NICHD) [E]" <[rowem@exchange.nih.gov](mailto:rowem@exchange.nih.gov)>  
**Subject:** RE: Additional SUPPORT study questions

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, October 21, 2013 2:53 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5) [redacted]

(b)(5) [redacted]

Thanks,

Renate

---

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
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- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

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Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Spong, Catherine (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 3:35:03 PM

I suggest you (b)(5)

(b)(5)

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:32 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

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Rosemary D Higgins, MD

Sent from my iPhone

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**Date:** October 21, 2013, 3:24:38 PM EDT  
**To:** "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Cc:** "Fine, Amanda (NIH/OD) [E]" <amanda.fine@nih.gov>, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>  
**Subject:** RE: Additional SUPPORT study questions

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**Sent:** Monday, October 21, 2013 2:53 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** FW: Additional SUPPORT study questions

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(b)(5)

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Renate

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

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Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Tyson, Jon E  
**To:** Susan Hintz  
**Cc:** [Abhik Das \(Adas@rti.org\)](mailto:Adas@rti.org); [Adas@rti.org](mailto:Adas@rti.org); [Higgins, Rosemary \(NIDH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIDH/NICHD); [Abbot Laptook \(alaptook@WTHRI.org\)](mailto:Abbot.Laptook@alaptook@WTHRI.org); [Wally Carlo \(wacarlo@uab.edu\)](mailto:WallyCarlo@uab.edu); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Walsh, Michele \(Michele.Walsh@UH-hospitals.org\)](mailto:Walsh.Michele@UH-hospitals.org)  
**Subject:** RE: Draft SUPPORT NEURO neuroimaging and 18-22 month outcomes manuscript  
**Date:** Monday, October 21, 2013 3:03:44 PM  
**Attachments:** [Hintz NEURO 18-22 mo - Manuscript\\_rev092113\\_CLEAN1.docx](#)

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Nice job, Susan! My comments are highlighted in yellow for whatever they may be worth. Sorry not to get them to you sooner.

As always it was great to see you at the Steering Committee meeting.

---

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Tuesday, September 24, 2013 3:56 PM  
**To:** Susan Hintz; Rosemary Higgins; Pat Barnes; Dorothy Bulas; Tom Slovis; Neil Finer; Lisa Wrage; das Das; Tyson, Jon E; David Stevenson; Wally Carlo, M.D.; Michele Walsh; laptook Laptook; Yoder; Krisa Van Meurs; ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Wade Rich; nancy newman; Helen Cheng  
**Cc:** Stephanie Archer  
**Subject:** Re: Draft SUPPORT NEURO neuroimaging and 18-22 month outcomes manuscript

Dear colleagues,

Thank you all for your extremely helpful input, comments, and insights over the past 2 weeks on this manuscript. I have attempted to integrate the many important points that have been raised. Attached are 3 documents - the revised manuscript with TRACK CHANGES, the revised manuscript CLEAN, and the tables. Note that there have been significant cuts to move toward the 2700 word limit, and substantial reorganization to the results and discussion. Also note that the follow up PIs are included in the authorship - authorship order is currently being determined.

Please provide final comments by **October 4th**.

Thanks you again for your commitment and dedicated work -

Susan

On Sep 11, 2013, at 2:36 PM, Susan Hintz <[srhintz@stanford.edu](mailto:srhintz@stanford.edu)> wrote:

Dear colleagues,

Attached is the SUPPORT NEURO cohort neuroimaging and 18-22 month outcomes manuscript and tables. This has been through RTI, an initial review by Rose, and is reflective of their comments and revisions. Our neuroimaging experts and central readers (Pat, Dorothy and Tom) are currently reviewing the manuscript.

Authorship order was determined by a combination of extent of involvement of this phase of the project, membership on the original subcommittee connected with the secondary proposal (MSCIDA project), and SUPPORT subcommittee.

Target journals that have been primarily discussed are NEJM and Pediatrics. The abstract is structured for NEJM, and both NEJM and Pediatrics require abstract length to be limited to 250 words. The manuscript itself remains too long, despite the fact that I have cut more than 700 words from previous drafts over the past weeks. Stepping back I can see some areas for potential further cuts, but I will await input from co-authors. As you know, NEJM limit is 2700, Pediatrics is 3000. There are 5 tables.

I look forward to your input and recommendations, which I would like to receive within 2 weeks (**September 25th**).

Thank you for your commitment and dedication to this ongoing study.

Susan

**Neonatal neuroimaging and neurodevelopmental outcomes at 18-22 months corrected age in extremely preterm infants: The SUPPORT NEURO Study**

Susan R. Hintz, MD MS Epi; Patrick D. Barnes, MD; Dorothy Bulas, MD; Thomas L. Slovis, MD; Neil N. Finer, MD; Lisa A. Wrage, MPH; Abhik Das, PhD; Jon E. Tyson, MD MPH; David K. Stevenson, MD; Waldemar A. Carlo, MD; Michele C. Walsh, MD MS; Abbot R. Laptook, MD; Bradley A. Yoder, MD; Krisa P. Van Meurs, MD; Roger G. Faix, MD; Wade Rich, RRT; Nancy S. Newman, RN; Helen Cheng, MS; **\*\*FOLLOW UP PIs from participating sites – order of authorship being determined\*\***; Rosemary D. Higgins, MD, for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

**ABSTRACT** (249 words)

**Background:** Extremely preterm infants are at high risk for adverse neurodevelopmental outcomes. Cranial ultrasound (CUS) is standard *unless you feel CUS has been demonstrated to improve outcomes, it would seem better to substitute:* usual practice for brain imaging in preterm infants, but MRI has been reported to better predict outcomes.

**Methods:** We performed a prospective study of early CUS, late CUS, and near-term MRI *suggest you insert something like: (each read by a central expert reader)* in a subcohort of infants born at 24-27+6/7 weeks gestation to relate neuroimaging findings including brain MRI white matter abnormality (WMA) and cerebellar lesions to outcomes at 18-22 months corrected age, and to assess the relative value of early CUS, late CUS and brain MRI, adjusting for perinatal/neonatal variables, to predict the composite outcomes of neurodevelopmental impairment (NDI) or death after all neuroimaging and severe gross motor impairment or death. *perhaps clearer to say... predict composite outcomes of later death or neurodevelopmental impairment or later death or severe gross motor impairment.*

**Results:** Of 480 infants, 15 died and 20 were lost. Increasing severity of WMA and significant cerebellar lesions on MRI were associated with adverse outcomes. Cerebellar lesions were identified by CUS in only 7 cases *? add:* of 72 identified by MRI. In full regression models, both late CUS and MRI, but not early CUS, remained independently associated with NDI or death (MRI significant cerebellar lesions: OR 3.1, 95% CI 1.4 – 7.0; late CUS: OR 12.9, 95% CI 3.4 - 48.1), and gross motor impairment or death. In models that did not include late CUS, moderate-severe WMA on MRI was also independently associated with both outcomes. *It is hard to know what to emphasize most. I wonder if it would be good to substitute for prior two sentences something like:* The area under the ROC was virtually identical either CUS or HUS

was used in conjunction with perinatal variable and early CUS for predicting NDI or death and for gross motor impairment or death at 18-22 mo.

**Conclusions:** Late CUS and brain MRI abnormalities identified by a central reader were associated with adverse 18-22 month outcomes, independent of early CUS and other factors, underscoring the relative importance of near-term neuroimaging. *Susan, with the small increase in AUC with either over that with perinatal and early CUS, critical reviewers may legitimately question the last phrase. You might want to just delete this phrase. Alternatively, given that most clinicians don't predict outcomes or counsel parents with a regression equation that includes all the variables used, might you want to refer here and above (and give more stress in the text) to the predictive value of MRI and CUS as a single predictor of outcome? Brain MRI may augment CUS in detection of cerebellar lesions. If space add (and if not, consider substituting for last sentence) something like: Whether school age outcomes is better predicted from MRI than late HUS remains to be determined.*

## INTRODUCTION

Cranial ultrasound (CUS) is currently the routine neuroimaging tool for preterm infants (1). Multiple neurodevelopmental outcomes studies have demonstrated associations of major CUS abnormality with adverse outcomes in very preterm infants, including cerebral palsy (CP) (2), but with widely varying designs in regard to CUS protocols and timing. Carefully performed studies of CUS and outcomes among very preterm infants have implicated white matter (WM) injury, not intracranial hemorrhage (ICH) alone, as a critical underlying finding linking abnormal CUS findings with adverse neurodevelopmental outcome (3-5). This, in part, has led to the concept that if WM injury is better characterized, it may be possible to better predict motor and developmental outcomes, anticipate needs, and devise interventions for prevention of injury or subsequent effects.

Brain magnetic resonance imaging (MRI) is more sensitive in detecting WM abnormalities (WMA) (6,7) than CUS. White matter injury on near-term MRI in preterm infants has been associated with brain maturational disturbances, as well as developmental and neuromotor impairment (8-10). Cerebellar injury seen by MRI but not by CUS may be associated with higher risk for neurologic abnormalities (11), although the importance of punctate lesions is unclear (12).

Despite what appears to be extensive experience with CUS and brain MRI in preterm infants, significant controversies and questions exist as to which neuroimaging study to perform, whether and when to perform them, and their relative values in prognosis. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) developed the Neuroimaging and Neurodevelopmental Outcomes (NEURO) Study, which was a secondary study to The Surfactant Positive Airway Pressure and

Pulse Oximetry Randomized Trial (SUPPORT). The NEURO study is, to our knowledge, the largest prospective study of neonatal CUS, near-term brain MRI, and neurodevelopmental outcomes in extremely preterm infants. Our objectives were to 1) relate near-term brain MRI findings of WMA and cerebellar lesions to neurodevelopmental outcomes at 18-22 months corrected age, and 2) to assess the relative value of early CUS, late CUS, and MRI, considering other perinatal/neonatal risk factors, to predict adverse outcomes. *Susan, the question you address is of course different if you are using blinded central readings than if you are using clinical readings reported from many different observers under clinical circumstances when they may be provided clinical information and can view prior studies. You might lead up to the statement of purpose by noting a need to compare the incremental predictive value of late CUS and MRI read by expert readers unobscured by expectations or interobserver differences.*

## METHODS

### Study design and population

The NEURO study was a secondary study to SUPPORT, which was a randomized, multicenter, 2x2 factorial trial of ventilation and oxygenation management strategies among 24-27+6/7 week estimated gestational age (EGA) infants (13,14). Infants eligible for the NEURO study were enrolled in SUPPORT at one of the 16 centers participating in the NEURO secondary, and consented for enrollment into the study. The SUPPORT trial enrolled infants born from February 2005 to February 2009, from 20 centers in the NICHD NRN. As a secondary to SUPPORT, the NEURO study was approved and began recruitment after SUPPORT began enrollment. Participating centers did not begin enrollment simultaneously. The serial neuroimaging required for inclusion in the study continued to near-term equivalent age; therefore

the NEURO cohort represents a selective subgroup of the overall SUPPORT cohort. Written informed consent to participate in NEURO was obtained either at the time of enrollment into SUPPORT, or separately. The study was approved by the institutional review boards (IRB) of all participating centers, and by the IRB of RTI International, the Data Coordinating Center for the NICHD NRN.

Trained research staff at each center collected data at each center, using definitions developed by NICHD NRN investigators, and described in previous publications (13-16). Data were transmitted to RTI International, the NICHD NRN data-coordinating center, which stored, managed, and analyzed all data.

#### Neuroimaging: Cranial US and brain MRI

Cranial US: An “early” CUS at 4-14 days, and a “late” CUS at 35-42 weeks postmenstrual age (PMA) were obtained for NEURO study participants. Cranial US imaging was obtained per local center clinical protocol. The NEURO study procedures specified only that 6 paracoronal and 5 parasagittal views through the anterior fontanelle was considered the minimum standard protocol for neonatal CUS. Mastoid, posterior fossa, or cine views were not required. Central reader interpretations were used for study analyses. Copies of early and late CUS were sent by centers to RTI International in digital or film format. Two masked central readers (DB, TS) reviewed all NEURO cohort CUS independently utilizing a modified central reading form used in previous NICHD NRN studies (17). A composite adverse finding on early CUS was defined as presence of grade III or IV intracranial hemorrhage (ICH) (18) or cystic periventricular leukomalacia (cPVL) on either or both sides. A composite adverse finding on late CUS was defined as cPVL, or porencephalic cyst, or moderate-severe ventricular enlargement (VE) on either or both sides, or a shunt. For all CUS, assessment of interobserver reliability

between central readers demonstrated  $\kappa=0.75$  for the early CUS composite adverse finding, and a  $\kappa = 0.88$  for the late CUS composite adverse finding. *When they disagreed, what was done?* Central readers also noted additional views performed including mastoid views, and presence of cerebellar or posterior fossa lesions.

Brain MRI: A conventional brain MRI was obtained at 35-42 weeks PMA, and within 2 weeks of late CUS. Minimum requirements included using a 1.5 T system, and necessary sequences included T1-weighted and T2-weighted sagittal and axial views, section thickness 3 mm and 0 gap; coronal SPGR, section thickness 1.5 mm; axial GRE, section thickness 3 mm. In the context of the NEURO study, it was advised that neonatal brain MRIs could be obtained without the use of sedation. Central reader interpretations were used for study analyses. Copies of MRIs were sent to RTI International by sites in digital or film format. A masked central reader (PB) reviewed all brain MRIs utilizing a central reader form that included WMA scoring according to a widely used classification system (6,8,19). Interrater agreement for moderate or severe WMA using this classification system has been reported to be 96% to 98% (8,19). *Kappa values available?* The central reader form also collected information regarding location, number, size, and imaging characteristics of lesions. Adverse findings on brain MRI were defined as moderate or severe WMA, or significant cerebellar lesions defined as lesions that were bilateral, cystic, and/or  $\geq 4$  mm in size.

#### Neurodevelopmental follow up assessments

At 18 to 22 months of age corrected for prematurity, infants underwent a comprehensive neurodevelopmental assessment, as described previously (20). Neurologic exams were performed by annually-certified examiners (21). Gross motor function was assessed with the Gross Motor Function Classification System (GMFCS) (22). Cerebral palsy (CP) was defined as

abnormal tone or reflexes in at least one extremity *and* abnormal control of movement or posture to a degree that interferes with age-appropriate activity. Children who had moderate-to-severe CP had a GMFCS level  $\geq 2$ . Cognitive development was assessed using the Bayley Scales of Infant Development, 3<sup>rd</sup> Edition (Bayley III) (23), performed by trained, annually certified examiners. Severe hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and severe visual impairment (defined as vision worse than 20/200) were based on examination and primary caregiver report. *What is appropriate to say about blinding or awareness of examiners for CUS and MRI?*

### Outcomes

Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, moderate or severe CP, GMFCS level  $\geq 2$ , severe hearing impairment, or bilateral severe visual impairment. Significant gross motor impairment was defined as moderate or severe CP or GMFCS of 2 or higher. Minimally impaired/unimpaired was defined as having all of the following: cognitive  $>85$ , no CP, without severe hearing impairment, and without bilateral severe visual impairment. The primary composite outcomes for multivariable analyses were NDI or death after all neuroimaging was obtained, and significant gross motor impairment or death after all neuroimaging obtained. These composite outcomes were selected because infants who died after all neuroimaging was performed but before 18 months corrected age could not be classified as having NDI or significant gross motor impairment.

### Statistical Analyses

The unadjusted associations between WMA, and the presence and severity of cerebellar lesions on MRI and neurodevelopmental outcomes were examined by chi square test, Fisher's exact test, or analysis of variance (ANOVA). To evaluate the relative predictive value of early CUS, late CUS, and MRI findings, we developed a series of generalized linear mixed models to predict the binary outcomes of death or NDI, and death or significant gross motor impairment using a stepwise selection approach with four sets of risk variables. The four risk variable groups selected before conducting any analyses *right?* were as follows: (1) Perinatal/neonatal risk factors: *you will want to spell out any abbreviations not defined previously* EGA (24-25+6/7 weeks vs. 26-27+6/7 weeks), race, male, multiple gestation, maternal insurance (public vs. other), late sepsis, BPD, PNS, surgery for PDA or NEC or ROP, and NRN center (entered as a random effect) *Partly because of the large number of centers, considered, this is a very large number of variables for the number of children with abnormality. Are these the final ones used or just the ones considered for use? If the variables differed in the different analyses, you will need to say so.* (2) Early CUS composite adverse finding; (3) Late CUS composite adverse finding; (4) MRI adverse findings, entered into the model separately, of moderate or severe WMA, and significant cerebellar lesions. Results of the models were expressed as odds ratios (OR) and 95% confidence intervals (CI). We then conducted receiver-operating characteristic (ROC) curve analyses from these models, and compared the predictive capabilities on the basis of the area under the curve (AUC) of the ROC curves. *Because likelihood ratios are (or should be) more meaningful to clinicians than AUC, particularly for continuous or graded outcome variables and because sensitivity and specificity are to some extent affected by prevalence of abnormality (which we are not sure is being understated by the Bayley III) though less so than positive and negative predictive values, I would think you would want to report here or at least in some*

*paper the likelihood ratios for degrees of abnormality (normal, mild, moderate, severe) for MRI if not also for HUS. Can you put in an appendix with other test characteristics?*

## RESULTS

There were 480 infants who had complete neuroimaging with late CUS and brain MRI within 2 weeks of each other. The mean (standard deviation) age at neuroimaging was as follows: early CUS, 8.1 (4.6) days; late CUS 37.4 (2.3) weeks PMA; brain MRI, 37.9 (2.3) weeks PMA. Late CUS and brain MRI were performed within 7 days in 93%. 15 infants died after all neuroimaging was obtained and before 18 months corrected age, and 20 were lost to follow-up. The outcome of NDI or death could be determined for 95% of the cohort (456/480) and significant gross motor impairment or death for 96% (460/480).

Selected demographic, perinatal and neonatal variables of the NEURO follow-up cohort are shown in Table 1. The rates of early or late CUS composite adverse findings were 10% and 5.8%, respectively. Among those who died before 18-22 months corrected age, 2 had early CUS adverse findings, 2 had late CUS adverse findings, 6 had moderate or severe WMA on brain MRI, and 4 had significant cerebellar lesions on MRI. *To assess the degree of potential selection bias, I would expect the reviewers will ask how this subcohort differs from all those who reached near term age in the trial. Wouldn't you want to show in the table?*

The rates of NDI and significant gross motor impairment were 8.6% and 3.8%, respectively. Among the 441 children for whom BSID III cognitive composite score was obtained, 26 (5.9%) scored less than 70, 98 (22%) scored less than 85, and the mean +/- SD score was 91.8 +/- 14. Among 445 children with neurosensory exams, moderate or severe CP was

diagnosed in 13 (2.9%), severe visual impairment in 3 (0.7%), and severe hearing impairment in 8 (1.8%).

Brain MRI findings and outcomes at 18-22 months are shown in Table 2. Increasing severity of WMA (Table 2A) and presence of cerebellar lesions (Table 2B) were associated with significantly lower mean BSID III cognitive scores, higher rates of cognitive scores less than 70 and less than 85, higher rates of moderate or severe CP, and lower rates of mildly/unimpaired status. Of note, cerebellar or posterior fossa lesions were seen by early or late CUS in only 7 cases, but mastoid views were included in only 48.2% of early CUS and 46.1% of late CUS as reported by central readers. Normal and major adverse composite findings on early and late CUS in relation to outcomes at 18-22 months are shown in Table 3.

In the full regression models, both late CUS composite adverse findings and MRI findings of significant cerebellar lesions remained independently associated with NDI or death, and with significant gross motor impairment or death, but not early CUS adverse findings or moderate or severe WMA on MRI (Table 4). However, in models without late CUS, MRI findings or moderate or severe WMA and MRI findings of severe cerebellar lesions remained independently associated with both outcomes (Table 4), but again, not early CUS adverse findings.

Predictive capabilities of the complete series of stepwise models were compared by the AUC of the ROC curves (Table 5). *Don't you need to explicitly specify Center (which is not usually thought of a perinatal/neonatal variable) to table? If center wasn't used in the analysis, I think the analyses should be repeated with center added, if necessary removing the other predictors.)* Compared with the models that included only perinatal/neonatal variables, the predictive capability of models was improved by the successive addition of early CUS adverse

findings, and late CUS adverse findings, and was best in models that included MRI. However, of note, 95% confidence intervals around the AUC for these models overlapped.

## DISCUSSION

In the largest prospective, extremely preterm neonatal neuroimaging and neurodevelopmental outcome cohort to date, we found that near term brain MRI and late CUS findings were associated with neurodevelopmental outcomes at 18-22 months. In full multivariable models, both late CUS adverse findings reflective of WM injury and significant cerebellar lesions by MRI remained independently associated with adverse outcomes. In models that did not include late CUS, MRI findings of both moderate or severe WMA and significant cerebellar lesions remained independently associated with outcomes. Early CUS findings were not associated with adverse outcomes when any late neuroimaging was taken into account. Our results underscore the value of understanding the trajectory and evolution of early brain injury in outcomes prediction, and suggest the need to revisit recommendations for near-term neuroimaging in the preterm infant.

Our findings concur with those of other investigators regarding the relative value of later neuroimaging findings indicative of WM injury compared with early findings alone. The Extremely Low Gestational Age Newborn (ELGAN) study found that only when accompanied or followed by WM lesions was intraventricular hemorrhage associated with increased risk for motor or developmental impairment at 2 years (4). The ELGAN study did not obtain MRI, so its potential added value cannot be assessed. Other preterm cohorts with both CUS and MRI imaging reported significant associations between MRI findings and outcomes, but either assessed CUS only for highest grade of ICH or cPVL rather than for later findings (8), or found

that any substantial abnormalities on MRI were detected by a carefully performed CUS done on the same day (24, 25). Others have reported that MRI may provide additive information to predict neuromotor outcomes (26), complementary to specific findings such as periventricular echodensities by CUS (27), or clinical neurologic exam findings (28, 29). The results of our comparative predictive analyses suggest that some type of near-term imaging – late CUS or brain MRI - adds value over perinatal/neonatal factors and early CUS alone. Predictive capability as measured by AUC of the ROC was best in models with all neuroimaging, but improvement with the addition of MRI was marginal.

The importance of cerebellar injury has become increasingly recognized in understanding of brain connectivity and neurodevelopmental impairment among children born extremely preterm, and is associated with neuromotor, behavioral, and cognitive delays (30, 31). The cerebellum can be visualized by CUS with mastoid views, but MRI may allow for a more complete visualization of location and extent of injury, and minor injury seen only by MRI. Our findings indicate that cerebellar injury was rarely seen by CUS; however, less than half of all study CUS had mastoid views. Detection could potentially have been improved by requiring a CUS protocol with more frequent and detailed imaging including mandatory mastoid and cine sequences. Nevertheless, similar to other reports (11), we found that cerebellar lesions by MRI were not uncommon, were typically missed by CUS, and the presence of significant cerebellar lesions by MRI was independently associated with adverse neurodevelopmental outcomes.

Although the limitations of early CUS findings have been reported, it is important to note that a substantial proportion of children with adverse near-term neuroimaging findings in our cohort did not have severe adverse neurodevelopmental outcomes at 18-22 months. Despite the strengths of our study, including a very large sample size, serial CUS and near term MRI

imaging, central reading, and a high follow-up rate, the selective subgroup, *is the word and or some other word(s) missing here?* low rates of adverse outcomes and of some adverse neuroimaging findings may have limited our power to assess associations. Furthermore, outcomes at 18-22 months cannot provide a nuanced picture of later childhood. Some recent analyses have reported moderate or severe WMA on neonatal MRI to be associated with cognitive delay, coordination impairment, and behavioral and psychiatric diagnoses (9,10, 32, 33) in later childhood. But such outcomes are complex and influenced by many factors. Thus, presenting neonatal neuroimaging results to families as singular predictive factors, and without a clear context of their limitations, is not appropriate (34). Whether findings on neonatal brain MRI can help to inform prediction of important later endpoints over and above CUS, other neonatal factors, and post-discharge environment, requires further study. Additional investigations are also warranted to determine if potentially improved prediction offered by MRI will be balanced by cost and other challenges, and by perceived value to families and providers. To that end, the NEURO cohort continues to be followed to school age.

White matter injury is an important link to brain development neurodevelopmental outcomes among very preterm infants (35). Although severe ICH on early CUS is strongly associated with accompanying or subsequent WM lesions, it is not an absolute relationship. A primary guideline for clinical neuroimaging screening in the United States recommends CUS for all infants less than 30 weeks EGA at 7–14 days, and only “optimally” again at 36–40 weeks (1). Unfortunately, an early CUS finding of severe ICH or cPVL is frequently the single adverse neuroimaging variable considered in prospective and retrospective studies of preterm neurodevelopmental outcomes, and often the primary focus in discussions with families of preterm infants. Based on our findings and those of other investigators, current routine

neuroimaging guidelines for very preterm infants should be re-evaluated to include expanded information and recommendations regarding near term neuroimaging, both for clinical and research purposes.

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: Tampa Bay Times article related to SUPPORT  
**Date:** Friday, October 25, 2013 9:54:59 AM

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Yes -- very nice!

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**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Sent:** Friday, October 25, 2013 9:53 AM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Tampa Bay Times article related to SUPPORT

Hi Rose, you've probably already seen this article...

## The parental consent dilemma: Saving extremely premature babies by signing forms

*By Kelley Benham*

*Tampa Bay Times*

October 18, 2013

Our baby was dying a half-dozen ways. She was born in the 23rd week of pregnancy weighing 1 pound, 4 ounces. Twiggy and translucent, her body heaved along with the mechanical whooshing of a ventilator that kept her alive while battering her lungs. No matter what the doctors did, she would probably end up dead or broken.

In the 196 days we sat by her bedside at All Children's Hospital, we signed consent forms allowing nurses to shove tubes down her throat and slip IVs into her thready veins. We consented to central lines that carry an overwhelming infection risk. We consented to chest tubes, blood transfusions and an operation so risky the surgeon fully expected it to kill her.

Signing those forms was my first official act as her mother, and the responsibility made my cheeks hot. But I didn't read a single one. The only thing I remember about any of those forms was how it felt to write next to my name that I was her mom.

Now the medical community is engaged in a furious debate about consent forms used in important pediatric research. Major studies conducted on babies like mine have come under attack from the consumer advocacy group Public Citizen, which says the research put babies at risk, and that parents were not adequately warned.

The debate has ensnared dozens of research institutions and just about every notable pediatric bioethicist in a fundamental debate over how to conduct research on the most vulnerable people on the planet. The government issued a scolding, the researchers and their supporters lashed back, and the critics are calling for review and derailment of current and future research.

This summer as I listened to hours of debate in which very smart people evoked Tuskegee and asked "How many babies must die?" it occurred to me that in all the bluster an essential truth was being lost.

All babies born so young are experiments. The rest is just paperwork.

...

At issue is a study performed on 1,300 extremely premature infants at 23 institutions from 2004 to 2009. Called the SUPPORT study, it was funded by the National Institutes of Health and approved by review boards at every participating institution. This was not the study of some radical treatment. Instead, it looked at already common treatments and asked which worked better. The implications are broad, because the Affordable Care Act mandates this sort of approach. Without it, treatment choices are more open to influence by gut, insurance payouts and lobbyists.

Doctors know that babies born with underdeveloped lungs need oxygen support to survive. But too much oxygen can wreck developing retinas and make babies blind. As doctors and nurses turn up the oxygen dial on a ventilator to help a struggling baby, they wonder if they are causing eye damage. As they dial it down and allow the baby to work harder to breathe, they wonder if they are damaging lungs or brains. So how much oxygen is the right amount?

Years of practice led to a consensus that a baby's blood oxygen level should be kept between 85 and 95 percent. Alarms sound if those targets are breached. For 6½ months, I sat by my baby's incubator and listened to those alarms, which became more urgent as my daughter struggled. I still hear them sometimes in my sleep.

When the study was designed, no one knew whether 85 percent was better than 95 percent, or where to find sweet spot in between. So researchers randomly sorted the babies into a low-oxygen group with a target of 85-89 percent or a high-oxygen group with a target of 91-95 percent. In a move that enraged critics, researchers rigged the monitors so doctors and nurses couldn't know which group each baby was in. Everyone thought they were aiming for the middle. If a baby was in the low oxygen group, for example, the oxygen saturation would read several points higher on the monitor. All babies stayed within

the range commonly accepted as safe.

Critics say it's bad for babies when their care is determined by research protocol, not the judgment of an individual doctor. They say that babies were undoubtedly harmed and that parents should have been warned on consent forms that babies in the low-oxygen group had a greater risk of dying.

But that argument makes a number of assumptions. The first is that researchers expected more babies in the low oxygen group to die, a claim they vigorously dispute. In fact, they say, clinical practice at the time trended toward lower oxygen, because the best evidence said it improved babies' vision without adverse effects. And all the eligible babies were at high risk of death or disability no matter what.

The second is that babies have a single Marcus Welby-type doctor who is certain of what he or she is doing. In reality, critically sick babies are cared for by a constantly rotating team of doctors, nurses, nurse practitioners, residents and specialists. Some are plain smarter or more experienced than others. Some know the baby better than others. Some treat aggressively and some don't. One doctor is pro-life. One has disabled kids. One was unexpectedly widowed. All of these factors influence how they talk to parents, how they assess quality of life and how they interpret risk.

For months I obsessed over my baby's oxygen saturation. The alarms would sound many times in an hour as our daughter struggled and recovered. She didn't hover inside the targeted range ordered by her physicians. She cascaded wildly. Gunk in a tube or even a loud noise or a song she didn't like on the radio would send her crashing. Sometimes all it took to bring her back was another round of the Hokey Pokey. "Keep singing!" our nurse would say. Other times I watched those numbers drop into the 20s as nurses lunged to revive her. Everyone who entered her room had a different threshold for when to intervene. Sometimes a doctor would turn the oxygen up, and as soon as they were gone, the nurse would turn it back down. All this came rushing back to me as I listened to the researchers talk about the "standard of care" as if it were something tangible and logical.

One day, while our baby was still small, one of our favorite doctors explained why it's so hard to know when to fiddle with the oxygen dial. He quoted off the top of his head from the recently completed SUPPORT study, the same study now under attack. He wondered aloud how many babies might go blind so one could live.

"I think about it every day and make my best guess," Dr. Rajan Wadhawan said. "If you're an exact person and a mathematician, it will drive you crazy."

It comforted me, though, to hear him quote that study. It made me feel like he brought more to it than his best guess. He brought an army.

"I stand on the shoulders of giants who came before me," he said.

I knew that before there were any studies, many babies died and were blinded by doctors making their best guesses. I asked Dr. Raj, as we called him, if he ever wondered if he was doing more harm than good. "Every day," he said.

I asked several more doctors the same question. They all gave the same answer.

...

Smart people disagree about whether the SUPPORT study was ethical or safe. It turns out that a few more babies in the low-oxygen group died, and a few more babies in the high-oxygen group developed short-term eye disease. But no matter how you measure it, babies in the study did better than babies not in the study. They had lower rates of blindness, disability and death. As a result of the study, doctors changed the way they treat very premature babies.

Our baby's doctors, while applying their best judgment and their very individual experiences, had broad shoulders to stand on. At other moments in our daughter's care, they had little data to guide them. One

doctor made a gutsy call to send our daughter to surgery based on faith and a look on our baby's face. We listened to doctors debate "What's the dose of this drug for a two-pound baby?" and no one was sure, because there was no study to consult. Our baby had to go first.

My daughter is 2 now, entirely healthy, saved from death, disability and blindness by a legion of doctors and nurses at All Children's Hospital to whom I owe a limitless debt. Had I been asked, I probably would have signed her up for a research study. If things had gone well, I might have believed the study had helped. If things had gone poorly, I might have blamed the study and feared I'd been duped. "Informed consent" is a holy grail in pediatric medicine, but I doubt it even exists. Someone would have approached me with another form. If it were a doctor who made eye contact or had a nice smile, I would have signed it.

I would not have read the form, because I did not read any of the forms, because the forms are for lawyers, not for parents. I had not slept in days. I was scared out of my mind. I had the mental capacity of a drunk being chased by bears. What kind of form can protect a parent in a situation like that?

In the time we lived in the NICU, we learned to accept risk. Just to enter that place is to embrace terror and uncertainty. There may be risk to participating in a study, but there is also risk to not participating. I don't believe that ethicists and doctors at two dozen institutions conspired to hurt babies. If they decide to tweak the language in their paperwork, so be it. But second-guessing and finger wagging should not hamstring further studies. At the frontier of human possibility, no form can make medicine a safe or predictable endeavor.

What protects our children most is solid research, and the wisdom drawn from babies who came before.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** 2 Explain the role of the SUPPORT study Data Safety Committee\_RAB cys  
**Date:** Tuesday, October 22, 2013 4:12:00 PM  
**Attachments:** 2 Explain the role of the SUPPORT study Data Safety Committee\_RAB cys.docx

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Here you go – a few minor tweaks

- *Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?*

(b)(5)

- *How many interim data checks were done during the SUPPORT study? What were the results?*

(b)(5)

Comment [SC(1)] (b)(5)  
(b)(5)

- *Were reports generated from these interim data checks? Please provide copies of these reports.*

(b)(5)

- ***Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?***

The information discussed at the DSMC meeting was confidential and not to be  
(b)(5)

- ***During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?***

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: DSMC confidentiality  
**Date:** Tuesday, October 22, 2013 2:00:57 PM

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The SUPPORT Trial recruitment was temporarily paused on November 23, 2005 based on concern regarding pulse oximeter readings > 95% and due to concern regarding separation of the two arms of the oximetry portion of the study. Further analyses were performed which showed that infants on room air accounted for a significant portion of pulse oximetry saturations above 95%. Separation of the two groups was reanalyzed based on time spent in room air and the duration of time spent at individual SpO2 values, which both showed group differences. The trial was restarted on February 6, 2006.

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 1:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: DSMC confidentiality

So they were concerned that having a reading greater than 95 percent was potentially harmful? And they thought they should only have one lower O2 group instead of a lower group and a higher group?

How was this resolved so the study could go forward?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 1:26 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: DSMC confidentiality

It was halted based :

on concern regarding pulse oximeter readings > 95% and due to concern regarding separation of the two arms of the oximetry portion of the study.

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 1:24 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: DSMC confidentiality

Just read the clinicaltrials.gov page about halting SUPPORT. The page doesn't mention why SUPPORT was halted.

Is there anything on line that talks about why it was halted?

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 1:23 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** DSMC confidentiality

Bob

The following sentence is in the NIH guidance:  
Protect the confidentiality of the trial data and the results of monitoring.

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

So the meeting minutes are the "results of monitoring" and should be kept confidential

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Raju, Tonse \(NIH/NICHD\) \[E\]](#); [Rowe, Mona \(NIH/NICHD\) \[E\]](#); [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Childress, Kerri \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION  
**Date:** Tuesday, October 22, 2013 1:24:38 PM

---

Bob and I just talked and he is revising

Thanks  
Rose

Rosemary D. Higgins, MD  
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-----Original Message-----

**From:** [Raju, Tonse \(NIH/NICHD\) \[E\]](#)  
**Sent:** Tuesday, October 22, 2013 1:24 PM  
**To:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#); [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Childress, Kerri \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

Agreed.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human  
Development National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

**From:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#)  
**Sent:** Tuesday, October 22, 2013 1:10 PM  
**To:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Raju, Tonse \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Childress, Kerri \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

Like Cathy's KISS – one simple suggestion in wording attached

**Mona**

**Mona Jaffe Rowe, M.C.P.**

**Associate Director for Science Policy,**

**Analysis and Communication**

**Eunice Kennedy Shriver National Institute of**

**Child Health and Human Development**

**National Institutes of Health, DHHS**

**Building 31, Rm 2A-18**

**31 Center Drive**

**Bethesda, MD 20892-2425**

**Phone: 301.496.1877/Fax: 301.496.0588**

**Email: rowem@mail.nih.gov <<mailto:rowem@mail.nih.gov>>**

**From: Spong, Catherine (NIH/NICHD) [E]**  
**Sent: Tuesday, October 22, 2013 11:09 AM**  
**To: Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]**  
**Cc: Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]**  
**Subject: RE: CONFIDENTAL SUPPORT DRAFT INFORMATION**

**My suggestions in track changes**

**Suggest** (b)(5)

**From: Raju, Tonse (NIH/NICHD) [E]**  
**Sent: Tuesday, October 22, 2013 10:51 AM**  
**To: Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]**  
**Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]**  
**Subject: RE: CONFIDENTAL SUPPORT DRAFT INFORMATION**

I think (b)(5)

My own take is just to say:

(b)(5)

Tonse N.K. Raju, MD, DCH

Chief, Pregnancy and Perinatology Branch

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

Phone: 301-402-1872, Fax: 301-496-3790

raju@mailto.nih.gov

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

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

Sent: Tuesday, October 22, 2013 10:43 AM

To: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]

Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E];

Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]

Subject: CONFIDENTIAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??

Let me know

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov) <<mailto:higginsr@mail.nih.gov>>

From: Childress, Kerri (NIH/NICHD) [E]

**Sent:** Monday, October 21, 2013 3:25 PM

**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]

**Subject:** RE: Additional SUPPORT study questions

**Importance:** High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

**From:** Myles, Renate (NIH/OD) [E]

**Sent:** Monday, October 21, 2013 2:53 PM

**To:** Bock, Robert (NIH/NICHD) [E]

**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]

**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com <mailto:SkeenK@cbsnews.com> ]

Sent: Monday, October 21, 2013 12:45 PM

To: Myles, Renate (NIH/OD) [E]

Subject: Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at [NICHDFOIARequest@mail.nih.gov](mailto:NICHDFOIARequest@mail.nih.gov) for assistance.

- How many interim data checks were done during the SUPPORT study? What were the results?
  
- Were reports generated from these interim data checks? Please provide copies of these reports.
  
- Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
  
- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

410-591-9567 cell

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

skeenk@cbsnews.com <<mailto:skeenk@cbsnews.com>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION  
**Date:** Tuesday, October 22, 2013 11:37:38 AM

---

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

From the above NIH notice:

Confidentiality must be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations.

Protect the confidentiality of the trial data and the results of monitoring.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:26 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

Rose, is there any on line guidance for how DSMCs should conduct themselves? I'd like to take another crack at (b)(5)

(b)(5)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:17 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: CONFIDENTIAL SUPPORT DRAFT INFORMATION

Can we talk sometime between 12-1PM?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03

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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:09 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

My suggestions in track changes

Suggest (b)(5)

---

**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

I think (b)(5)

My own take is just to say:

(b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:43 AM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD)

[E]

Subject: CONFIDENTIAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??

Let me know

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

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301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

From: Childress, Kerri (NIH/NICHD) [E]

Sent: Monday, October 21, 2013 3:25 PM

To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]

Subject: RE: Additional SUPPORT study questions

Importance: High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

From: Myles, Renate (NIH/OD) [E]  
Sent: Monday, October 21, 2013 2:53 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
Subject: FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,

Renate

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Monday, October 21, 2013 12:45 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
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- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: CONFIDENTIAL SUPPORT DRAFT INFORMATION  
**Date:** Tuesday, October 22, 2013 11:17:15 AM  
**Attachments:** Explain the role of the SUPPORT study Data Safety Committee cvs.docx

---

Can we talk sometime between 12-1PM?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 11:09 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

My suggestions in track changes  
Suggest (b)(5)

---

**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 10:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL SUPPORT DRAFT INFORMATION

I think (b)(5)

(b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch

Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, October 22, 2013 10:43 AM  
To: Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
Cc: Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
Subject: CONFIDENTIAL SUPPORT DRAFT INFORMATION

See attached – perhaps a phone conference would help??  
Let me know

Thanks

Rose

Rosemary D. Higgins, MD

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

From: Childress, Kerri (NIH/NICHD) [E]  
Sent: Monday, October 21, 2013 3:25 PM  
To: Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]  
Subject: RE: Additional SUPPORT study questions  
Importance: High

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

From: Myles, Renate (NIH/OD) [E]  
Sent: Monday, October 21, 2013 2:53 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
Subject: FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

(b)(5)

Thanks,

Renate

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Monday, October 21, 2013 12:45 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: Additional SUPPORT study questions

Renate,

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Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

- *Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?*

(b)(5)

- *How many interim data checks were done during the SUPPORT study? What were the results?*

(b)(5)

Comment [SC([1]:(b)(5)

(b)(5)

- *Were reports generated from these interim data checks? Please provide copies of these reports.*

(b)(5)

- *Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?*

(b)(5)

- *During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?*

Page 0529 of 2000

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** confidential  
**Date:** Tuesday, October 22, 2013 9:05:47 AM  
**Attachments:** Explain the role of the SUPPORT study Data Safety Committee.docx

---

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Willinger, Marian (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 9:04 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: I am upstairs at a meeting

Anytime- I'm in my office.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 22, 2013 8:11 AM  
**To:** Willinger, Marian (NIH/NICHD) [E]  
**Subject:** I am upstairs at a meeting

I can break away to talk to you this am – any time before 10 am is good

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Bcc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 4:16:18 PM

---

I have until tomorrow and will get your input

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 3:38 PM, "Raju, Tonse (NIH/NICHD) [E]" <rajut@mail.nih.gov> wrote:

My thoughts too. I also felt that the (b)(5)

(b)(5)

Also that (b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
rajut@mail.nih.gov

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

**From:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions

I suggest you (b)(5)

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:32 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

I need some advice here- at each point the (b)(5) How do we respond and should (b)(5) be involved? Both Alan and I have talked to the CBS reporters and there have been many questions answered via email

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

From: "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>  
Date: October 21, 2013, 3:24:38 PM EDT  
To: "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
Cc: "Fine, Amanda (NIH/OD) [E]" <amanda.fine@nih.gov>, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>  
Subject: RE: Additional SUPPORT study questions

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

From: Myles, Renate (NIH/OD) [E]  
Sent: Monday, October 21, 2013 2:53 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Cc: Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
Subject: FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity to (b)(5)

Thanks,

Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Monday, October 21, 2013 12:45 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- How many interim data checks were done during the SUPPORT study? What were the results?
- Were reports generated from these interim data checks? Please provide copies of these reports.
- Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
- During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

skeenk@cbsnews.com

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Willinger, Marian (NIH/NICHD) [E]  
**Bcc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Additional SUPPORT study questions  
**Date:** Monday, October 21, 2013 4:14:36 PM

---

Stoll in the meeting and scheduled to talk soon- I can talk to you at 5 or tomorrow.

I don't need to respond until tomorrow

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 3:48 PM, "Willinger, Marian (NIH/NICHD) [E]" <willingm@exchange.nih.gov> wrote:

Can you give me a call?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 3:32 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Fwd: Additional SUPPORT study questions

I need some advice here- at each point the (b)(5) [redacted]  
How do we respond and should (b)(5) [redacted] be involved? Both Alan and I have talked to the CBS reporters and there have been many questions answered via email

Rosemary D Higgins, MD

Sent from my iPhone

Begin forwarded message:

**From:** "Childress, Kerri (NIH/NICHD) [E]" <kerri.childress@nih.gov>  
**Date:** October 21, 2013, 3:24:38 PM EDT  
**To:** "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Cc:** "Fine, Amanda (NIH/OD) [E]" <amanda.fine@nih.gov>, "Rowe, Mona (NIH/NICHD) [E]" <rowem@exchange.nih.gov>  
**Subject:** RE: Additional SUPPORT study questions

Rose, hoping you can help us out here. Bob is on leave today, so if you can take a look at the questions below, we will do our best to keep Kim happy.

Thank you so very much, Kerri

---

**From:** Myles, Renate (NIH/OD) [E]

**Sent:** Monday, October 21, 2013 2:53 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Fine, Amanda (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Subject:** FW: Additional SUPPORT study questions

Hi Bob:

More questions from Kim Skeen on the SUPPORT trial. This might be a good opportunity (b)(5)

(b)(5)

Thanks,  
Renate

---

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Monday, October 21, 2013 12:45 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** Additional SUPPORT study questions

Renate,

We have a few additional questions for our story on the SUPPORT study. Here are our questions:

- <!--[if !supportLists]--> <!--[endif]--> Explain the role of the SUPPORT study Data Safety Committee? Explain NIH's role in overseeing the Data Safety Committee's work?
- <!--[if !supportLists]--> <!--[endif]--> How many interim data checks were done during the SUPPORT study? What were the results?
- <!--[if !supportLists]--> <!--[endif]--> Were reports generated from these interim data checks? Please provide copies of these reports.
- <!--[if !supportLists]--> <!--[endif]--> Were any trends found during the interim data checks? If so, what were these trends? What actions were taken as a result of any trends?
- <!--[if !supportLists]--> <!--[endif]--> During the SUPPORT study, did the Data Safety Committee see any evidence of an increased mortality rate for babies on the low end of the oxygen study? If so, what action was taken? If no action was taken, why not?

Please provide a response to our questions as soon as possible. Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Bcc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Clearance | Ambalavanan, Association of PaCO2 with outcomes in SUPPORT  
**Date:** Monday, October 21, 2013 2:51:43 PM

---

I did talk to her about this one before the furlough

Rosemary D Higgins, MD

Sent from my iPhone

On Oct 21, 2013, at 2:40 PM, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov> wrote:

We should probably ping Mona about this one too. It was submitted for clearance 9/4.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 12:12 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Clearance Tracking: Journal Article/Scientific Manuscript Clearance Request Awaiting Your Action

This is in Mona's cue – do you want me to call her??

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 12:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Clearance Tracking: Journal Article/Scientific Manuscript Clearance Request Awaiting Your Action

For Ambal's paper, it went in as Track #2. Cathy approved it with a note that "given this is a support paper recommend ospac triage it as well." Now it hasn't gone forward anywhere since 9/6. Who should I contact to get a final approval?

**From:** NICHDWorkflow

**Sent:** Wednesday, September 04, 2013 2:44 PM

**To:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** Clearance Tracking: Journal Article/Scientific Manuscript Clearance Request Awaiting Your Action

The following request for clearance is awaiting your action: Request ID: 14147 Request Type: Journal Article/Scientific Manuscript Title: Association of PaCO<sub>2</sub> with outcomes in SUPPORT (Ambal)(NRN) Requestor: NIH\archerst Branch/Center/Division: DER / PPB Status: Requestor Edits You may access the system at: <https://insider.nichd.nih.gov/clearancetracking>

**From:** Luc Brion  
**To:** Wrage, Lisa Ann; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** (b)(6)@gmail.com  
**Subject:** RE: Jackie LeVan's paper  
**Date:** Monday, October 21, 2013 12:41:43 PM  
**Attachments:** Jackie LeVan Manuscript NRN 10-21-13.docx

---

Rose et al:

I attach a revised version of the manuscript, which includes your comments and better addresses limitations of the study.

Luc

---

**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Monday, October 21, 2013 9:17 AM  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion  
**Cc:** (b)(6)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Yes, looks good. Actually it is pretty informative to me as I was not in on the discussion re: the survey.

Luc: I'll be working on the highlighted items.

Thanks.

Lisa

---

**From:** Das, Abhik  
**Sent:** Monday, October 21, 2013 10:11 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Luc Brion'; Wrage, Lisa Ann  
**Cc:** (b)(6)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Looks good to me.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, October 21, 2013 8:51 AM  
**To:** 'Luc Brion'; Wrage, Lisa Ann  
**Cc:** Das, Abhik; (b)(6)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Luc and others – please look over my additions and let me know if we should be more specific.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch

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MSC 7510  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
**Sent:** Friday, October 18, 2013 3:46 PM  
**To:** Wrage, Lisa Ann  
**Cc:** Das, Abhik ([adas@rti.org](mailto:adas@rti.org)); Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) @gmail.com  
**Subject:** RE: Jackie LeVan's paper

Lisa:

Thanks a lot for your help.

I edited the response to reviewers and the text of the manuscript.

In figure 1, the main difference is the % of outborn patients, this does not bias the results since we only used inborn patients in SUPPORT and in this cohort study.

Would you please respond to the 5 remaining queries which I have highlighted with yellow background?

Thanks a lot and best regards,

Luc

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 18, 2013 11:03 AM  
**To:** Luc Brion  
**Subject:** RE: Jackie LeVan's paper

Hi Luc,

I am glad your presentation went well.

I've attached your updated figure with a couple of comments included.

Please let me know if you have questions.

Thanks.

Lisa

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
**Sent:** Thursday, October 17, 2013 4:17 PM  
**To:** Wrage, Lisa Ann  
**Subject:** Re: Jackie LeVan's paper

Thanks a lot.

I was told the presentation went well.

Luc

Sent from my iPhone

On Oct 17, 2013, at 2:01 PM, "Wrage, Lisa Ann" <[wrage@rti.org](mailto:wrage@rti.org)> wrote:

Hi Luc,

I hope your presentation went well. Yes, I will work on Figure 1, I have another paper submission-related 'deadline' tomorrow and once I've met that I'll work on that figure.

Thanks.

Lisa

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]

**Sent:** Thursday, October 17, 2013 1:44 PM

**To:** Wrage, Lisa Ann

**Subject:** Jackie LeVan's paper

Lisa:

I have presented the reviewers' comments and potential additional analyses.

I attach the revised proposed response to reviewers, in which I trimmed requests to you to a minimum.

Could you please complete figure 1? I would appreciate it.

Rose will look at this and will give additional suggestions.

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaelyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1,4</sup> Roy Heyne, MD,<sup>1</sup>  
Mambarambath Jaleel,<sup>1</sup> MD, Neil Finer, MD,<sup>5</sup> Waldemar A. Carlo, MD,<sup>6</sup>  
Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: <sup>1</sup>Department of Pediatrics, University of Texas Southwestern, Dallas, TX; <sup>2</sup>Current affiliation: Pediatrix Medical Group, San Antonio, TX; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>4</sup>Current affiliation: The Ohio State University - Nationwide Children's Hospital; <sup>5</sup>Division of Neonatology, University of California, San Diego, CA; <sup>6</sup>Division of Neonatology, University of Alabama, Birmingham, AL; <sup>7</sup>Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; <sup>8</sup>Eunice Kennedy Shriver National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu  
No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Statement: No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: ~~197250~~ words

Article length: ~~2,410,697~~ words

Revised ~~109/108713~~/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## Abstract

### Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased by 15% after compare medical care practices and neonatal outcomes before and after publication of SUPPORT withiwithin NICUs in NRN centers.

### Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. ~~The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.~~

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ~~ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)~~

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

Conclusions:

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

### **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if ~~publication of SUPPORT was temporally associated with changes in~~ clinical practice, specifically ~~in the~~ proportion of preterm inborn infants intubated in the DR, ~~decreased~~ ~~changed after~~ SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a 15% decrease ~~lower proportion of~~ in ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT, using a conservative estimate based on preliminary data at Parkland Memorial Hospital. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. ~~The most important neonatal outcomes were se included~~ the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. ~~We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes~~ changed after SUPPORT.

## Methods

### Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important sSecondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP at discharge, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of

bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): ~~BPD, severe ROP and other ROP outcomes~~, death within 12 hours or by 36 weeks PMA, DR ~~practice outcome~~, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

#### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>46</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and

all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5-137-156</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Sample size analysis:

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%.<sup>14</sup> Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a 15% relative risk reduction in ETI from 80% to 68% with an alpha error less than 5% and a power greater than 99%, even if more than 50% of the patients met exclusion criteria. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

## Results

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). ~~Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a~~ total study population included of 3,849 infants:

1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1<sup>†</sup>.

There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2<sup>‡</sup>). The adjusted risk of DR ETI (~~adjusted RR 0.88, 95% CI 0.85-0.91~~) significantly decreased after ~~publication of~~ SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2<sup>‡</sup>). The adjusted risk of BPD/death (~~adjusted RR 0.94, 95% CI 0.89-0.99~~), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge, (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP, (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 22). In contrast, the adjusted risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only. the appendix. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

#### Discussion:

Infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was four times as

~~large as the ARR in DR-ETI observed in very low birth weight infants in the Vermont Oxford Network over a 10-year span between 2000 and 2009 (3.7%; 95% CI 4.2% to 3.3%).<sup>18</sup> The ARR over a 10-year span in the NRN and Vermont Oxford Network was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (50%). In this study we compared data before SUPPORT with data after SUPPORT and did not thus we were unable to analyze serial changes in whether the decrease in proportion of ETI in each participating centers. The proportion of ETI in each center could have decreased with increasing use of CPAP and experience with teek place at the time of introduction of and increasing experience with T-piece connectors before, during or after participation in ,conduction-of the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation the trial, or after publication of the results of SUPPORT. The proportion of ETI in at Parkland Memorial Hospital, one of the centers participating in SUPPORT, decreased in non-enrolled patients from baseline before SUPPORT (2003-20054) to epochs during SUPPORT (2005-2009) and before its publication (20096-201009);<sup>17</sup> ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).<sup>16</sup> In one of the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after introduction of bubble CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR-ETI observed in this study. Lack of correlation between We had hypothesized that the change in the proportion in ETI after SUPPORT and would be greater in centers with high-baseline ETI proportion; although the correlation did not reach significance, this~~

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~~may have resulted from the limited number of centers included in this study and from the narrow range (82-97%) of and from the fact that 9 of the 11 centers had pre-SUPPORT proportions of ETI in 9 of 11 centers that varied within a narrow range of about 82-97%.~~ and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database ~~and of inborn patients~~ which limits incomplete/missing data and information bias, ~~and~~ the use of multivariate analysis to take into account ~~differences in~~ confounding variables ~~between the two periods~~, ~~the use of inclusion and exclusion criteria that were similar to resembled (though did not exactly match)~~ those used in SUPPORT, and the inclusion of ~~We were able to analyze center-specific changes after SUPPORT as well as changes in the entire sample, because we only used~~ ~~We elected to limit for this study to centers that~~ remained in the NICHD NRN during the two cohorts, thereby limiting bias due to l:

~~because of large inter-institutional differences that have been observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample.~~

However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which prevents any cause-effect interpretation; the which could introduce changes in patient population; strict selection criteria; high percentage of exclusions; lack of serial data and of data from centers that did not participate in SUPPORT but remained in the NRN during the study period, thereby preventing analysis of secular trends; lack of information on the history of changes in policies and practice guidelines in each participating NRN center; the limited number of variables included in the GDB, and secular trends and lack of information in the . Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in the primary

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~~outcomes of SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p-value < 0.05 just by chance; thus p-values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB on did not include information on individual use of DR CPAP, oxygen saturation targets in the DR or the NICU, or the rationale used for each various practice in each infant, s used for each patient in each center. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.~~

~~Since we did not adjust p-value for multiple comparisons, secondary and tertiary variables should all be considered as exploratory. Mortality The risk of death before discharge was significantly decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>19</sup> and between 2003 and 2007.<sup>18,19,20</sup> but It is~~

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~~consistent with a recent review a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011.~~<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21,24</sup>

~~This study was not designed to test whether any change in secondary or tertiary variables were associated with changes in O2 saturation or with the application in practice of evidence from SUPPORT or from other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies.~~

~~We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since serial oxygen saturation measurements were not prospectively collected in the GDB before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Several center-specific practice guidelines and policies may have individual practice may have changed between the two epochs, based on new information on other studies rather than SUPPORT, e.g., antenatal DR studies on and NICU management and outcomes antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup>~~

~~synchronized nasal intermittent positive pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>22-31,29</sup> We considered conducting a survey of clinical practices in the 11 NRN centers participating in this study. We decided not to so because information in queries is usually obtained from an individual physician or nurse responding to the request from the network and may not be reflective of all practitioners at individual sites. Experience in the network has shown that such surveys often are not very accurate even on current practices. DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies.~~

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors during SUPPORT and with tight oxygen monitoring and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

#### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ~~ROP/death,~~ BPD/death, and death before discharge in for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial

compared to a period before SUPPORT. ~~The adjusted risk of severe BPD and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower in SUPPORT.~~

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~~Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.~~

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**Jaelyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Luc P Brion:** Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

**Lisa Wrage:** Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

**Marie Gantz:** Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Myra H Wyckoff:** Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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**Roy Heyne:** Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011);

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Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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**Figure Legends**

**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

Figure 1

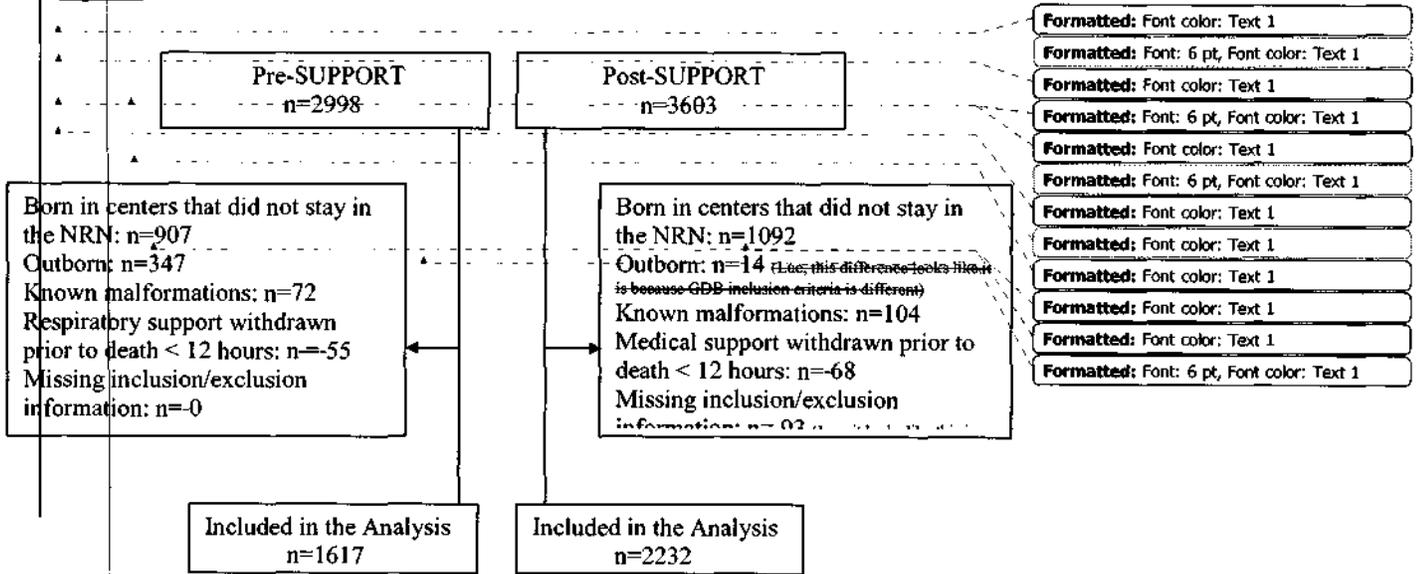
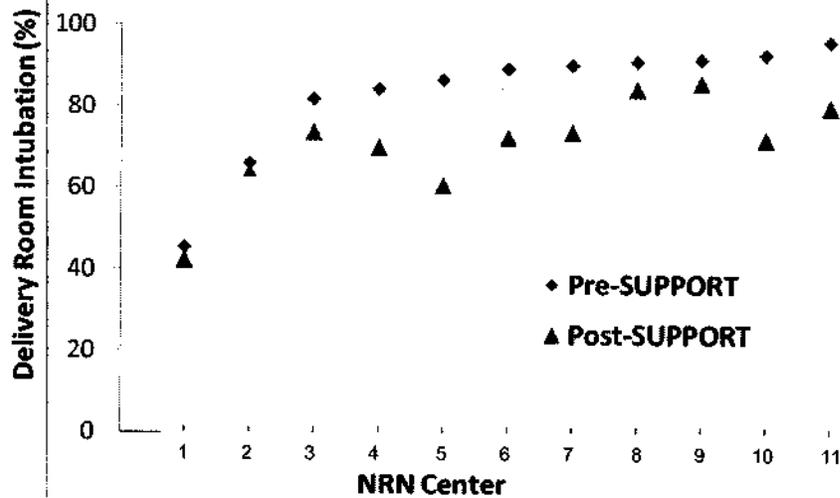


Figure 2



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**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192 (14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42/1617 (2.6)	120/2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

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Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup> The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post- SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>4</sup></b>
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	=	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	=	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	=	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	=	1.04 (0.97-1.1)	0.26
Severe ROP by discharge	174/1294 (13.5)	181/1873 (9.7)	0.0009	=	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	=	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	=	0.90 (0.84-0.97)	0.003
Days on ventilator (survivors) until discharge	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1,-3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 3- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup>The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup>survivors to discharge or 120 days, whichever came first, max is 120 days.

**From:** Luc Brion  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann  
**Cc:** (b)(5)@gmail.com  
**Subject:** RE: Jackie LeVan's paper  
**Date:** Monday, October 21, 2013 10:30:27 AM  
**Attachments:** Responses to reviewers\_102113.docx

---

I agree, thanks a lot, Rose.

I attach the responses to reviewers document with all changes accepted.

Luc

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Monday, October 21, 2013 9:11 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion; Wrage, Lisa Ann  
**Cc:** (b)(5)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Looks good to me.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, October 21, 2013 8:51 AM  
**To:** 'Luc Brion'; Wrage, Lisa Ann  
**Cc:** Das, Abhik; (b)(5)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Luc and others – please look over my additions and let me know if we should be more specific.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
**Sent:** Friday, October 18, 2013 3:46 PM  
**To:** Wrage, Lisa Ann

**Cc:** Das, Abhik (adas@rti.org); Higgins, Rosemary (NIH/NICHD) [E]; (b)(5)@gmail.com  
**Subject:** RE: Jackie LeVan's paper

Lisa:

Thanks a lot for your help.

I edited the response to reviewers and the text of the manuscript.

In figure 1, the main difference is the % of outborn patients, this does not bias the results since we only used inborn patients in SUPPORT and in this cohort study.

Would you please respond to the 5 remaining queries which I have highlighted with yellow background?

Thanks a lot and best regards,

Luc

---

**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]

**Sent:** Friday, October 18, 2013 11:03 AM

**To:** Luc Brion

**Subject:** RE: Jackie LeVan's paper

Hi Luc,

I am glad your presentation went well.

I've attached your updated figure with a couple of comments included.

Please let me know if you have questions.

Thanks.

Lisa

---

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]

**Sent:** Thursday, October 17, 2013 4:17 PM

**To:** Wrage, Lisa Ann

**Subject:** Re: Jackie LeVan's paper

Thanks a lot.

I was told the presentation went well.

Luc

Sent from my iPhone

On Oct 17, 2013, at 2:01 PM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Hi Luc,

I hope your presentation went well. Yes, I will work on Figure 1, I have another paper submission-related 'deadline' tomorrow and once I've met that I'll work on that figure.

Thanks.

Lisa

---

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]

**Sent:** Thursday, October 17, 2013 1:44 PM

**To:** Wrage, Lisa Ann  
**Subject:** Jackie LeVan's paper

Lisa:

I have presented the reviewers' comments and potential additional analyses.

I attach the revised proposed response to reviewers, in which I trimmed requests to you to a minimum.

Could you please complete figure 1? I would appreciate it.

Rose will look at this and will give additional suggestions.

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

Ref.: Ms. No. 20131573

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial  
The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members is a separate Appendix file. The figure is at 1000 dpi. We labeled the third table as online only. We include an itemized list of responses to the reviewers.

We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.

*Response: The text of the first version had 2697 words; the revised version has 2410 words. The text of the discussion was shortened by ½ page. We have shortened the results section by removing all numbers from the text that were in Figure 1 or in the tables.*

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.ipeds.com/authorinfo>).

*Response: We have shortened the abstract; it contains 197 words. The abstract is structured as indicated.*

Please upload the list of Study Group members as a separate Appendix file.

*Response: the list of Study Group is a separate file.*

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

*Response: Figures are submitted at TIFF files with 1,000 dpi.*

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the

figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

*Response: we have changed online documents as requested.*

**Itemized responses to Reviewers:**

(b)(4),(b)(6)

**Comments:**

(b)(4),(b)(6)

(b)(4),(b)(6)

**Minor comments:**

(b)(4),(b)(6)

(b)(4),(b)(6)

Reviewer #2: (b)(4),(b)(6)

(b)(4),(b)(6)

Specific comments:

(b)(4),(b)(6)

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(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 0590 of 2000

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(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

Page 0591 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

## **Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, October 21, 2013 9:15 AM  
**To:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Manuscript #13-551 Decision  
**Attachments:** ROP Natural History Study Manuscript (for resubmission to J Perinatol).doc; J Perinatology Response Letter.doc; Acknowledgments (Supplement for ROP Natural History Study Manuscript).docx; Figure 1.pdf; Figure 2.pdf; Figure 3.pdf; Figure 4.pdf; ROP Natural History Study Manuscript (for submission to J Perinatol).doc

Bob and Mona

As a heads up, This secondary study from the SUPPORT trial has been provisional accepted for the Journal of Perinatology. We looked at the eye exams done as part of the SUPPORT trial to evaluate the current recommendations from the AAP to guide physician practice. The data from the SUPPORT trial show that the eye exam recommendations are current, should not be changed, but close follow up after discharge is warranted for infants who go home with either active disease or immature blood vessels in their retina.

Let me know if you need more information. Dr. Kennedy will provide us with the galley proofs when she gets them.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Friday, October 11, 2013 12:58 PM  
**To:** [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Wrage, Lisa Ann ([wrage@rti.org](mailto:wrage@rti.org))  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Manuscript #13-551 Decision

Here's the provisional email acceptance from J Perinatol. There aren't any substantive criticisms. I've attached a drafted response letter. There were very few changes made to the manuscript (highlighted in yellow). Many of the suggestions either didn't make sense to me or were asking for adding things that were already there. I tried to be diplomatic in the response (also attached) – mostly just specifying where the information is. Let me know if you have suggestions or if you understand any of the suggestions better than I did. I've attached the previously submitted and updated versions of the manuscript for you to compare if you want.

I'm not sure I understand what the reviewer is trying to say in #15 but, as I look at these numbers again (last row in Table 4), I don't think they make an important point. I think we should take them out of this table and count them differently in

(b)(5)

isa, could you please add (b)(5) to the x-axis for the most recent version of Figure 2? I've added the (b)(5) by copying it from a prior iteration of the manuscript. Could you please verify that the numbers are correct? I also have a question for you in the comment in the revision.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

**From:** [jperinatol@us.nature.com](mailto:jperinatol@us.nature.com) [mailto:[jperinatol@us.nature.com](mailto:jperinatol@us.nature.com)]  
**Sent:** Monday, September 23, 2013 10:17 AM  
**To:** Kennedy, Kathleen A  
**Subject:** Manuscript #13-551 Decision

22nd Sep 2013

Dear Dr. Kennedy:

Manuscript #: 13-551  
Title: Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants  
Author: Dr Kennedy

The initial review of your manuscript is complete. I am happy to inform you that the manuscript may be accepted for publication if it is revised extensively according to our suggestions. Below are the reviewers' comments that indicate their concerns. Both reviewers were enthusiastic about the manuscript, one provides numerous suggestions for improvement.

In addition I would appreciate how the manuscript may be shortened in its print version by converting some of the Tables or the Acknowledgement to Supplementary Materials. The three page single spaced listing of the institutions and various committees would consume 4 print pages and seems especially eligible to be fine for electronic only publication. If supplied as Supplemental Materials it would still be available to all readers - since most readers will download the text from electronic sources they can easily also receive the supplemental material.

Within the next three months, please resubmit the revised manuscript online together with a summary of your responses to the reviewer comments. Be sure to include your Conflict of Interest statement in the manuscript. The manuscript will be read within the office and then may be resent to the outside reviewers for further evaluation.

If we do not receive the revised manuscript within three months the file will be closed and any subsequent resubmission would be treated as a new manuscript. Please notify us should you decide to withdraw the manuscript from further consideration.

Click on the link below to submit the revision online (or highlight, copy and paste all the information between the < > symbols).

<http://mts-jper.nature.com/cgi-bin/main.plex?el=A1BX7CFI6A7Bmw3J6A9sMZv4iLf6KzPt9u7LQJXQZ>

Thank you for submitting this paper to the Journal of Perinatology.

Sincerely,

Edward E. Lawson, M.D.  
Editor-in-Chief  
the Journal of Perinatology  
Johns Hopkins Medicine  
600 N. Wolfe St  
Baltimore, MD 21287

-----  
Reviewer #1 (Comments to the Author):

Abstract

(b)(4),(b)(6)

(b)(4),(b)(6)

**Reviewer #2 (Comments to the Author):**

(b)(4),(b)(6)

This email has been sent through the NPG Manuscript Tracking System NY-610A-NPG&MTS

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### **Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants**

Kathleen A. Kennedy, MD MPH<sup>1</sup>; Lisa A. Wrage, MPH<sup>2</sup>; Rosemary D. Higgins, MD<sup>3</sup> Neil N. Finer, MD<sup>4</sup>; Waldemar A. Carlo, MD<sup>5</sup>; Michele C. Walsh, MD MS<sup>6</sup>; Abbot R. Laptook, MD<sup>7</sup>; Roger G. Faix, MD<sup>8</sup>; Bradley A. Yoder, MD<sup>8</sup>; Kurt Schibler, MD<sup>9</sup>; Marie G. Gantz, PhD<sup>2</sup>; Abhik Das, PhD<sup>10</sup>; Nancy S. Newman, RN<sup>6</sup>; Wade Rich, RRT<sup>4</sup>; Dale L. Phelps, MD<sup>11</sup>; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

**Address correspondence to:**

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Richard W. Mithoff Professor of Pediatrics  
UT-Houston Medical School  
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**Running title:** Retinopathy of Prematurity Screening Criteria

**Funding source:** The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT trial.

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<sup>2</sup> RTI International, Research Triangle Park, NC

<sup>3</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

<sup>4</sup> University of California at San Diego, San Diego, CA

<sup>5</sup> Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

<sup>6</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>7</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>8</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

<sup>9</sup> Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH

<sup>10</sup> RTI International, Rockville, MD

<sup>11</sup> Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

## **Abstract**

**Objective:** To determine if current retinopathy of prematurity screening guidelines<sup>1</sup> adequately identify treatable ROP in a contemporary cohort of extremely low gestation infants.

**Study Design:** Data from the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial were used. Inborn infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age with consent prior to delivery were enrolled in 2005-2009. Severe retinopathy of prematurity (Type 1 retinopathy of prematurity or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the randomized trial. Examinations followed then current American Academy of Pediatrics screening recommendations.<sup>2,3</sup>

**Results:** 1316 infants were enrolled in the trial. 997 of the 1121 who survived to first eye exam had final retinopathy of prematurity outcome determined. 137 (14% of 997) met criteria for severe retinopathy of prematurity and 128 (93%) of those had sufficient data (without missing or delayed exams) to determine age of onset of severe retinopathy of prematurity. Postmenstrual age at onset was 32.1 to 53.1 wks. In this referral center cohort, 1.4% (14/997) developed severe retinopathy of prematurity after discharge.

**Conclusion:** Our contemporary data support the 2013 AAP screening guidelines for ROP for infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age.<sup>1</sup> Some infants do not meet treatment criteria until after discharge home. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

**Keywords (not in title):** extremely premature infant

## **Introduction**

Timely detection of treatable retinopathy of prematurity (ROP) is necessary to optimize outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1,4</sup> are based on natural history data from the CRYO-ROP<sup>5</sup> and LIGHT-ROP<sup>6</sup> studies. The CRYO-ROP study<sup>7</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, but it was conducted over 20 years ago (1986-1987). The LIGHT-ROP trial enrolled infants from 1995-1997.<sup>8</sup> Over the past two decades, survival of lower birth weight infants in the US and other developed countries has increased.<sup>9,10</sup> For infants 501-750 g birth weight, survival increased from 41% in 1990-1991 to 55% in 1997-2002.<sup>9</sup> The timing of onset of ROP is related to both gestational age (GA) and chronological (postnatal) age.<sup>5</sup> It rarely occurs before 30 weeks postmenstrual age (PMA, sum of GA at birth and chronological age) or before 4 weeks chronological age. Current American Academy of Pediatrics (AAP) recommendations are for screening to begin by 31 weeks PMA for infants born at 22-27 weeks.<sup>1</sup> The impact of increased survival of extremely low birth weight (ELBW) infants on the incidence and timing of the onset and regression of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "CRYO-ROP threshold"). In the CRYO-ROP study, the earliest identification of CRYO-ROP threshold disease was 32.6 weeks postmenstrual age.<sup>6</sup> Based on the results of the ET-ROP trial, treatment is now recommended for Type 1 ROP, defined as stage 3 in zone I or plus disease with any ROP in zone I, or stage 2 or 3 with plus disease in zone II. Since Type 1 ROP occurs earlier in the course than CRYO-ROP threshold ROP, it is important to determine if screening criteria developed for CRYO-ROP threshold ROP are still appropriate for reliable timely

identification of Type 1 ROP.<sup>11</sup> There have been several more recent publications of the incidence and timing of ROP onset. The ET-ROP trial<sup>12</sup> and a population-based cohort study of infants born 2004-2007 in Sweden<sup>13</sup> reported the age of onset of stages 1, 2, and 3 ROP; however, the age distribution of onset of Type 1 ROP was not reported in either publication. A recent publication from Canada reported the age of onset of Type 1 ROP in a cohort of 214 infants  $\leq 27$  weeks gestation;<sup>14</sup> this cohort included only 24 infants with Type 1 ROP. A recent publication from a German cohort<sup>15</sup> reported that "No preterm infants required treatment before the 33rd postmenstrual week or 8th postnatal week, respectively"; the age distribution was not reported. We need updated information about the evolution of ROP in a large contemporary cohort to determine when screening must be initiated to capture all infants as Type 1 ROP develops. Type 2 ROP (stage 1 or 2 ROP without plus disease in Zone I, or stage 3 ROP without plus disease in Zone II) is less severe but warrants close follow up for possible progression to Type 1 ROP. Therefore we also looked at the age of onset of Type 2 ROP.

In addition to information about when screening should begin, clinicians need information about when an infant is no longer at risk for severe ROP so that appropriate follow-up can be arranged (particularly for infants who are ready to be discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the CRYO-ROP threshold criteria had done so by 45.9 weeks postmenstrual age.

This analysis was designed to describe the natural history of ROP in a recent cohort (born 2005-2009) of inborn infants 24-27<sup>6/7</sup> weeks gestational age who were enrolled in the NICHD Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT)<sup>16</sup> to determine if the current ROP screening guidelines are still appropriate to identify Type 1 ROP in a contemporary cohort of infants.

## Methods

In the SUPPORT trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, severe ROP [defined as Type 1 ROP or treatment with laser ablation, cryotherapy, bevacizumab (monoclonal antibody to vascular endothelial growth factor) injection, scleral buckle, or vitrectomy] or death before discharge was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design trial. ROP outcome data were prospectively collected for all enrolled infants.<sup>16</sup> Inborn infants 24<sup>0/7</sup> – 27<sup>6/7</sup> weeks gestation (no birth weight limits) were eligible for this trial if prenatal consent was obtained, there were no known congenital malformations, and full resuscitation was planned. Study eye examinations were performed by each site's ophthalmologists. Ophthalmology exams began no later than 31-33 weeks postmenstrual age, as recommended in the AAP guidelines that were in place when the study began.<sup>2,3</sup> Subsequent inpatient and outpatient exams were conducted according to the ophthalmologists' established screening procedures at each center. The following data were recorded for each eye at each exam: the date of the eye exam, the highest stage of ROP in the lowest zone, the highest stage of ROP in any zone, the presence of plus disease, and whether the infant met the criteria for Type 1 ROP. Study eye exam data were recorded for each exam until one of the study endpoints: death; severe ROP (Type 1 or worse ROP or ROP treated with surgery or bevacizumab injection as detailed above) in either eye; or no severe ROP (full vascularization to the ora serrata or vascularization in zone III (without severe ROP) on 2 consecutive exams. Required ROP follow-up (including exams after hospital discharge) was curtailed at 55 wks PMA.

Postmenstrual age was calculated as gestational age at birth (weeks+days using the best obstetrical estimate) plus the chronological age in weeks+days at the time of each exam. For this

observational study, "age of onset" was defined as the postmenstrual or chronological age at which ROP or ROP of a given severity was detected, with the recognition that onset was some time interval prior to detection. Infants with Type 1 ROP whose first exam with Type 1 ROP was preceded by a gap of more than 2 weeks (or more than 1 week if the previous exam had ROP in zone I) between exams were defined as having an uncertain age of onset. No infants had Type 1 ROP on the initial exam. Infants who did not complete exams according to the study schedule (adjudicated ROP outcomes) were not included in this observational study. In cases where the findings differed between eyes, the age of onset was recorded as the earliest age at which the ROP criteria were met in either eye.

Categorical outcomes were compared using Chi square tests; continuous outcomes were compared using t-tests or Wilcoxon tests where appropriate. Non-parametric confidence limits are provided for continuous data grouped into quantiles.<sup>17</sup> Cumulative incidence curves for age of onset of severe ROP and age of maturity were compared by gestational age subgroups (26-27 weeks vs. 24-25 weeks) using Kolmogorov-Smirnov tests. All analyses were performed using SAS v. 9.2 (SAS Institute, Cary, NC).

## Results

1316 infants were enrolled in the SUPPORT trial from 2005-2009 and 1091 survived to ROP determination (Figure 1). Among infants who survived to ROP determination, 91% (997/1091) had a definitive ROP outcome; 94 of the ROP outcomes were adjudicated. Sixty-four percent (643/997) of these infants developed ROP and 14% (137/997) developed severe ROP. Among infants with severe ROP, 93% (128/137) had sufficient data (no missing or delayed exams prior to "onset" exam) to determine the age of onset of ROP.

The baseline demographic characteristics of the infants with and without ROP are shown in Table 1. As expected, infants with ROP were lower birth weight and more frequently non-Hispanic White as compared to infants without ROP. The risk of ROP by gestational age, in this cohort, is depicted in Figure 2. As expected, the likelihood of having no ROP increased and the likelihood of having severe ROP decreased with each increasing week of completed gestation at birth (Figure 2).

Several previously reported risk factors for ROP are shown in Table 2.<sup>18,19,20</sup> Consistent with prior observational studies, as compared to infants without ROP, infants with ROP had a longer duration of supplemental oxygen and more frequently had late onset sepsis, fungal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus ( $p < 0.05$  for all comparisons of no ROP vs any ROP).

For infants who had any ROP and had a known age of onset, the cumulative distribution for the age of onset is displayed in Table 3. Of note, 25% of severe ROP was identified after 38.6 weeks postmenstrual age and 5% was identified after 43.3 weeks. For the 9 infants with severe ROP and uncertain age of onset, the age of identification ranged from 33.7-40.0 weeks PMA. The distributions for onset of ROP were examined separately (not shown) for infants in each of the treatment arms (lower oxygen saturation and higher oxygen saturation target ranges) and the distributions were similar so only the combined data are shown. The distributions for age of onset of severe ROP for each two-week interval of completed gestation at birth are shown in Figure 3. In contrast to prior studies,<sup>5</sup> our data did not show an inverse relationship between gestational age at birth and chronological age at onset of treatable ROP. PMA of onset of severe ROP is significantly later for GA groups 26-27 weeks vs. 24-25 weeks ( $p < 0.01$ ). There is no

significant difference in the distribution of chronologic age of onset between these two GA groups.

The age at which the retinal vessels matured to the point of minimal risk of progression to severe ROP (to the ora serrata or two consecutive exams with vessels in zone III without stage 3 or plus disease) is shown in Figure 4 for infants who never had ROP and for infants who had mild or moderate ROP (ROP that did not meet criteria for severe ROP). The cumulative distributions are shown by postmenstrual age and by chronological age, plotted separately for each completed week of gestation at birth. Among infants who had one exam with vessels recorded as in Zone III (but not to the ora serrata), 2/251 infants subsequently developed severe ROP. Retinal vessels reached final favorable status several weeks later in infants with mild or moderate ROP as compared to infants who never had ROP. The distributions of PMA and chronologic age at maturity were significantly different for infants with mild/moderate ROP vs. infants with no ROP, both overall and within GA groups ( $p < .0001$ ).

The proportions of infants who had severe (Type 1 or treated) ROP identified after discharge or transfer are shown in Table 4. Infants with severe ROP identified after discharge had onset of ROP at a later postmenstrual age and were discharged at an earlier postmenstrual age than infants who had severe ROP identified before discharge. In this referral center cohort of 997 infants, 1 infant (0.1%; or 0.7% of 137 infants with severe ROP) was diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit (while still in the hospital); 14 (1.4% of the cohort; or 10% of infants with severe ROP) reached severe ROP after discharge home. To explore whether infants at high risk of developing severe ROP after discharge could be identified before discharge, we compared the last pre-discharge exams (Table 5) and clinical risk factors (Table 6) for infants who did and did not develop severe ROP after discharge (among

**Comment [KKA1]:** Some of our proportions have caused confusion for the reviewers and likely will be confusing to readers as well. I've tried to include the denominators for our calculations to make things more clear. One possible source of confusion is that we're using 137 as a denominator here instead of the 128 who had known age of onset. I think that's ok as long as we know that none of the 9 infants who did not meet our study criteria for known age of onset had severe ROP identified while they were still in the hospital. Lisa, could you please verify that?

infants whose exams had not reached final favorable status at the time of discharge). While infants with vessels in Zone I or with ROP in Zone II on the last pre-discharge exam were at the highest risk for developing severe ROP after discharge (1/4=25% and 10/206=5%, respectively), 1 case of severe ROP after discharge (1/82=1%) occurred in an infant with ROP in Zone III on the last exam before discharge. Infants who developed severe ROP after discharge were slightly lower birth weight and lower gestational age and treated with supplemental oxygen longer, but we did not identify any clinical risk factors in our data that clearly identify infants at risk to develop severe ROP after discharge.

#### **Discussion**

Current screening guidelines are based on studies conducted over 20 years ago. Earlier treatment of ROP has been recommended since 2004,<sup>11</sup> so updated information regarding the timing of onset of ROP is needed. While our study findings differ from previous studies<sup>5</sup> in that the chronologic age of ROP onset was not later in lower GA infants, our findings still support the 2013 screening guidelines for infants 24-27 6/7 weeks gestation at birth.

In the CRYO-ROP natural history study,<sup>5</sup> lower birth weight infants developed treatable ROP at a later chronological age than larger infants, such that the incidence curves for birth weight strata were superimposed when plotted by postmenstrual age. This observation led to a recommendation by the AAP that ROP screening could be delayed until 31 weeks postmenstrual age, regardless of gestational age at birth,<sup>1</sup> albeit with a caution that the data supporting the recommendation included very few 22-23 week infants. This relationship (later postnatal onset in lower gestational age infants) was not apparent in our data. There are several potential explanations for this difference. Firstly, the gestational age range of infants in our study was

relatively narrow because our cohort was selected by gestational age. The CRYO-ROP cohort was selected by birth weight ( $\leq 1250$  g) and therefore included a wider gestational age range and a relatively high proportion (20%) of infants who were small for gestational age.<sup>21</sup> Although both the CRYO-ROP and SUPPORT trials used obstetrical criteria, if available, for assigning gestational age, the more recent SUPPORT trial relied more heavily on early ultrasound criteria. If the CRYO-ROP trial more often used pediatric exam criteria, this could have resulted in a systematic overestimate of gestational age<sup>22</sup> and in a systematic bias toward more stable lower risk infants having gestational age overestimated. In our data, age of onset was related to chronological age as well as PMA such that onset of severe ROP occurred at a slightly earlier postmenstrual age in more immature infants.

The more recent studies of the timing of onset of ROP have had inconsistent findings regarding the relationship of onset with chronologic vs postmenstrual age. In the study by Austeng et al,<sup>13</sup> which included 22-26 week GA infants, the more immature infants developed ROP (any ROP) at an earlier PMA than more mature infants. The study by Isaza et al<sup>14</sup> included 23-27 week infants; infants  $\leq 25$  weeks GA developed any ROP at the same mean PMA (later mean chronologic age) than infants  $>25$  weeks. In this study, the onset of Type 1 ROP occurred at an earlier PMA and at an earlier chronologic age in the less mature infants. In our data, the median age of onset of Type 1 ROP (50% cumulative incidence in Figure 3) occurred at an earlier PMA in the less mature (24-25 week) infants, whereas the medians for chronologic age are similar.

For the purpose of screening (not missing cases of treatable ROP), the earliest and latest ages of onset of Type 1 ROP are more important than the mean or median age. We did not observe severe ROP before 6 weeks chronological age or before 32 weeks PMA. These findings are

consistent with the other recent studies. In the Canadian study,<sup>14</sup> the earliest onset of Type 1 ROP was 6 weeks chronological age or 32.7 weeks PMA. In the study by Muether et al<sup>15</sup> that included 767 infants 22-35 weeks gestation, no infants required treatment before 8 weeks chronologic age or 33 weeks PMA. Together these studies provide no evidence that current screening guidelines should be changed to accommodate earlier (Type 1 ROP) treatment, although we still have limited data for 22-23 week GA infants.

For clinicians who care for infants in tertiary referral centers, an important question is whether infants are still at risk for treatable ROP when they are otherwise ready to be discharged or transported to a lower acuity neonatal unit closer to home. We have not identified any other studies that reported the risk of treatable ROP occurring after discharge home. While it was not a common occurrence in our study (1.4% of the cohort and 14% of the infants with severe ROP), the potential consequences could be severe if infants who are still at risk for treatable ROP are lost to follow up after discharge. We were not able to identify any risk factors or combination of risk factors that would distinguish these infants from others who had not reached retinal maturity at the time of hospital discharge.

This observational study has several important limitations. We were unable to generate true population incidence data from this cohort because only consented inborn infants were included. This consented enrolled cohort differed from the non-enrolled populations in participating sites in that the proportion receiving antenatal steroids was higher and the proportion of Caucasians was higher.<sup>23</sup> The SUPPORT trial inclusion criteria limit the generalizability of these data to infants < 24 weeks gestation who are at even higher risk of ROP or to infants > 27 <sup>6</sup>/<sub>7</sub> weeks. The ophthalmology exams for this study were performed by site ophthalmologists according to AAP recommendations but with no additional training or standardization for the study. This might

lead to more inconsistency or random error than would occur under strict study exam protocols, but it more closely reflects what typically occurs in clinical practice.

Current AAP screening guidelines, published in 2013,<sup>1</sup> recommend that ROP screening should begin by 31 weeks postmenstrual age and continue until vessels have reached zone III for infants without previous zone I or II ROP, until full vascularization to the ora serrata for infants treated with bevacizumab, until 50 weeks postmenstrual age for infants without prethreshold ROP, or until ROP has regressed. In our cohort, the postmenstrual age at onset of severe ROP ranged from 32.1 to 53.1 wks, although only 1 infant developed severe ROP after 45 weeks. Our data therefore do not support a change in the 2013 screening guidelines. In this referral center cohort of 997 infants, 0.1% (0.7% of those with severe ROP) were diagnosed with severe ROP after back transfer to a lower acuity neonatal intensive care unit; 1.4% (10% of infants with severe ROP) reached severe ROP after discharge. Post-discharge follow-up of infants who are still at risk for severe ROP is crucial for timely detection and treatment.

Future population-based studies are needed to better inform the optimal windows for ROP screening in extremely premature infants, particularly those less than 24 weeks and more than 27 weeks gestation at birth. These studies are difficult because they require strict adherence to screening protocols and careful documentation of all eye exams in a large number of infants to identify the full spectrum of age at onset. While randomized trials most often employ such rigorous data collection methods, they are often limited by selection bias that is introduced by the consent process for trials.<sup>23</sup>

**Conflict of Interest:** The authors declare that they have no financial interests related to the work described in this manuscript.

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**Figure Legends:**

Figure 1. Flow diagram of subjects in the original trial and current analysis

Figure 2. Risk of ROP by gestational age at birth (in completed weeks) among all SUPPORT trial infants with known outcome (997 survivors + 223 infants who died)

Figure 3. Postmenstrual and chronological age of onset for severe (Type 1 or treated) ROP (among infants with age of onset determined) by gestational age at birth with 95% confidence intervals (shaded areas)

Figure 4. Postmenstrual and chronological age of "favorable outcome" (vessels to the ora serrata or vessels in Zone III on two consecutive exams) by gestational age at birth

Table 1. Baseline characteristics of infants in SUPPORT Trial and observational study

	Infants Enrolled in SUPPORT Trial	Infants Included in Observational Study (Reached Final ROP <sup>1</sup> Outcome)			
		All ROP Outcomes	By ROP Outcome Category		
			No ROP	Mild/Moderate ROP	Severe (Type 1 or Treated) ROP
n	1316	997	354	506	137
Gestational age, wks [mean (SD) <sup>2</sup> ]	26.2 (1.1)	26.3 (1.1)	26.8 (0.9)	26.2 (1.0)	25.4 (0.9)
Birth weight, g [mean (SD)]	830 (193)	849 (190)	943 (173)	823 (180)	704 (142)
Small for gestational age <sup>3</sup> [n (%)]	173 (13)	117 (12)	22 (6)	65 (13)	30 (22)
Race/ethnicity [n (%)]					
Non-Hispanic Black	489 (37)	374 (38)	154 (44)	179 (35)	41 (30)
Non-Hispanic White	521 (40)	398 (40)	125 (35)	212 (42)	61 (45)
Hispanic	259 (20)	190 (19)	69 (19)	93 (18)	28 (20)
Other	47 (4)	35 (4)	6 (2)	22 (4)	7 (5)
Male [n (%)]	712 (54)	529 (53)	195 (55)	256 (51)	78 (57)
Antenatal steroids [n (%)]	1265 (96)	955 (96)	341 (96)	480 (95)	134 (98)
Multiple birth [n (%)]	337 (26)	253 (25)	91 (26)	121 (24)	41 (30)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Standard deviation

<sup>3</sup> Based on Olsen<sup>24</sup> growth curves

Table 2. Risk factors for ROP<sup>1</sup>

Risk Factor	No ROP <sup>2</sup>	Any ROP (Mild, Moderate, or Severe)	Mild/ Moderate ROP	Severe (Treated or Type 1) ROP
n	354	643	506	137
Days on supplemental oxygen <sup>3</sup> [median (IQR <sup>4</sup> )]	33 (10, 60)	66 (39, 100)	59 (31, 94)	95 (68, 119)
Late-onset sepsis (+ culture) [(n (%))]	75 (21)	247 (38)	171 (34)	76 (55)
Fungal sepsis [n (%)]	2 (0.6)	23 <sup>5</sup> (4)	15 <sup>5</sup> (3.0)	8 (5.8)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	29 (8)	98 <sup>5</sup> (15)	69 <sup>5</sup> (14)	29 (21)
Proven necrotizing enterocolitis <sup>6</sup> [n (%)]	20 (6)	72 (11)	54 (11)	18 (13)
Patent ductus arteriosus (medical or surgical) [n (%)]	123 (35)	366 (57)	271 (54)	94 (69)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> p<0.05 for all comparisons of No ROP vs Any ROP (mild, moderate, or severe)

<sup>3</sup> Tabulated until 120 days or discharge if discharged sooner, among infants who survived to discharge, transfer or 120 days

<sup>4</sup> Interquartile range

<sup>5</sup> Missing data for 1 infant

<sup>6</sup> Modified Bell's stage II or III<sup>25</sup>

Table 3. Postmenstrual and chronological age of onset<sup>1</sup> [with 95% confidence intervals (CI<sup>2</sup>)] of any stage ROP<sup>3</sup> (among infants with ROP age of onset determined)

		Cumulative Percent with Onset of ROP								
ROP type	n	Min <sup>4</sup>	1%	5%	25%	50%	75%	95%	99%	Max <sup>4</sup>
Postmenstrual Age (weeks)										
Any ROP (95%CI)	634	29.3	30.4 (29.6-30.7)	31.4 (31.1-31.4)	32.7 (32.4-32.9)	33.9 (33.7-34.0)	35.1 (34.9-35.4)	38.0 (37.3-38.7)	41.0 (39.9-43.6)	46.7
Type 2 ROP <sup>5</sup> (95%CI)	158	29.3	29.7 (29.3-30.7)	31.1 (30.6-31.7)	34.3 (33.6-34.9)	36.1 (35.7-36.9)	38.1 (37.6-38.7)	40.4 (39.9-43.7)	46.4 (43.3-46.9)	46.9
Severe (Type 1 /treated) ROP (95% CI)	128	32.1	32.7 (32.1-32.7)	33.9 (32.7-34.3)	35.1 (34.7-35.4)	36.4 (35.7-36.9)	38.6 (37.4-40.0)	43.3 (41.0-45.0)	45.0 (44.4-53.1)	53.1

		Cumulative Percent with Onset of ROP								
ROP type	n	Min	1%	5%	25%	50%	75%	95%	99%	Max
Chronological Age (weeks)										
Any ROP (95%CI)	634	4.0	4.6 (4.1-4.7)	5.4 (5.0-5.6)	6.9 (6.6-6.9)	8.0 (7.7-8.1)	9.4 (9.1-9.6)	11.9 (11.3-13.0)	15.3 (14.4-18.0)	19.7
Type 2 ROP <sup>3</sup> (95%CI)	158	4.4	4.6 (4.4-5.6)	6.3 (4.7-6.6)	8.7 (7.9-9.6)	10.8 (10.3-11.4)	12.6 (12.0-13.1)	15.0 (14.1-19.6)	21.0 (17.0-22.7)	22.7
Severe (Type 1 /treated) ROP (95% CI)	128	6.4	7.1 (6.4-7.9)	8.4 (7.1-8.9)	9.8 (9.3-10.3)	11.3 (10.6-11.7)	13.1 (12.4-14.4)	17.0 (16.1-19.0)	19.0 (18.9-28.4)	28.4

<sup>1</sup> Age of onset is defined as the age at which the specified type of ROP was first observed while following the study monitoring protocol. For “Any ROP”, this is the first exam with any stage of ROP in any zone.

<sup>2</sup> Confidence interval

<sup>3</sup> Retinopathy of prematurity

<sup>4</sup> Min = minimum age at which designated severity of ROP was identified; max = maximum age.

<sup>5</sup> Type 2 ROP is defined as stage 3 in zone II, no plus disease or stage 1 or 2 in zone I, no plus disease. (85 of these infants had ROP that regressed and 73 infants later developed severe ROP.)

Table 4. Postmenstrual age of severe ROP<sup>1</sup> onset and discharge for infants with severe ROP determined before and after discharge home

Infants with Severe ROP N=137	First exam with severe ROP occurred <u>before</u> discharge to home n=123	First exam with severe ROP criteria occurred <u>after</u> discharge to home n=14
Postmenstrual age at first occurrence of severe ROP: weeks [median, range]	36.0 (32.1-45.0)	40.9 (37.9-53.1)
Postmenstrual age at discharge: weeks [median, range]	42.5 (37.7-78.3)	38.3 (36.4-51.3)
First occurrence of severe ROP after transfer to lower acuity hospital [n]	1	4

<sup>1</sup> Retinopathy of prematurity

Table 5. ROP<sup>1</sup> exam (most recent) prior to discharge for infants with final ROP status determined after discharge home

Worst findings in either or both eyes on last exam prior to discharge:	Severe ROP Group N=14	No Severe ROP Group N=535
Vessels in zone I [n (%)]	1 (7.1%)	3 (0.6%)
Lowest zone of vessels=II and any stage ROP in any zone [n (%)]	10 (72%)	196 (37%)
Lowest zone of vessels=II and no ROP [n (%)]	2 (14%)	126 (24%)
Lowest zone of vessels=III and any stage ROP in any zone [n (%)]	1 (7%)	81 (15%)
Lowest zone of vessels=III and no ROP [n (%)]	0	121 (23%)
Plus disease [n (%)]	0	0
No exam prior to discharge [n (%)]	0	3
Unknown (missing or incomplete information on exam prior to discharge) [n (%)]	0	5

<sup>1</sup> Retinopathy of prematurity

Table 6. Risk factors for ROP<sup>1</sup> for infants with final ROP status determined after discharge home

Risk Factor	Severe ROP Group N=14	No Severe ROP Group N=535
Birth weight, g [mean (SD)]	701 (103)	872 (185)
GA <sup>2</sup> at birth, wks [mean (SD)]	25.7 (0.9)	26.4 (1.0)
Days on oxygen [mean (SD)]	59 (27)	47 (33)
Early onset sepsis [n (%)]	0	10 (2)
Late onset sepsis [n (%)]	7 (50)	148 (28)
Fungal sepsis [n (%)]	1 (7)	12 (2)
Grade 3-4 intraventricular hemorrhage or periventricular leukomalacia [n (%)]	0	59 (11.1)
Proven necrotizing enterocolitis [n (%)]	1 (7)	36 (7)
Patent ductus arteriosus [n (%)]	11 (79)	258 (48)
Discharge on oxygen [n (%)]	2 (14)	88 (16)

<sup>1</sup> Retinopathy of prematurity

<sup>2</sup> Gestational age



**Medical School**  
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Kathleen A. Kennedy, MD, MPH  
*Richard W. Mithoff Professor of Pediatrics*  
*Director, MS in Clinical Research Degree Program*

October 10, 2013

Edward E. Lawson, MD  
Editor  
c/o Sue Ann Nelson  
75 Varick Street, 9<sup>th</sup> Floor  
New York, NY 10013

Dear Dr. Lawson:

The authors thank the reviewers for their careful review of the attached manuscript entitled "Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants". The following changes were made to address the reviewers' suggestions:

1. The reference for the 2013 screening guidelines was moved to the abstract as requested. Additional detail about the guidelines could not be added to the abstract without exceeding the word limit for the abstract. The criteria for beginning screening are delineated in the first paragraph of the Introduction.
2. The sentence in the conclusion has been qualified to apply to infants eligible for the SUPPORT trial.
3. The 137 infants with severe ROP was also given as a % of infants with ROP determination. The numerator and denominator are specified for the 1.4%.
4. Two references are cited for the AAP screening recommendations that were in place at the time of the study.
5. This suggested sentence has been added to the Conclusion in the Abstract.
6. See #2 above.
7. We don't understand what interval is being requested. In this study (done after the ET-ROP study) infants were treated when they developed Type 1 ROP so they did not progress to CRYO threshold ROP.
8. Type 1 ROP is defined in the second paragraph of the Introduction.
9. Details about the ROP exams are in the first paragraph of the Methods.
10. The drug category for bevacizumab has been specified in the first paragraph of the Methods. The types of ROP interventions that were included as treatment are also detailed in the first sentence of this paragraph. This sentence is referenced later in the paragraph (second-to-last sentence) where the term "surgery" is used. This sentence also states that severe ROP was defined when the criteria were met in either eye.
11. "Gestational Age" has been added to the x-axis for the Figure 2.
12. The "Any ROP" column has been added to Table 2.
13. A "Cumulative Percent" row title has been added to Table 3. Another sentence has been added to the fourth paragraph of the Results to highlight the important findings in Table 3. We have used the



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- terms postmenstrual age and chronological age as recommended by the AAP (Engle WA et al. Age terminology during the perinatal period. Pediatrics 114: 1362-1364, 2004.)
14. The shaded areas have been designated in the legend for Figure 3.
  15. The numbers in the last row of Table 4 have been removed and the differences between the two groups have been highlighted in the text (last paragraph in Results). *(may need to change this if decide to try to include numbers for severe ROP after discharge in infants who were back transferred)*
  16. The description of the data in Table 5 in the text has been expanded and expressed differently in the last paragraph of the Results to highlight ROP exam findings that put infants at the highest risk for severe ROP after discharge.
  17. It isn't entirely clear what "magnitude estimate" is requested. We restated the percent of infants who were diagnosed with severe ROP after discharge in the fifth paragraph of the Discussion.
  18. The lack of training for examiners has now been added to the paragraph about limitations.

The Acknowledgments section has been moved to a Supplement as requested. There is a conflict of interest statement in the manuscript.

These changes have undoubtedly improve the clarity of the manuscript. We again thank the reviewers and editors for their suggestions and consideration.

Sincerely,

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Director, MS in Clinical Research Degree Program  
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## Acknowledgments

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Dr. Marie Gantz, and Ms. Wrage (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

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University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Michael J. Acarregui, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

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Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel

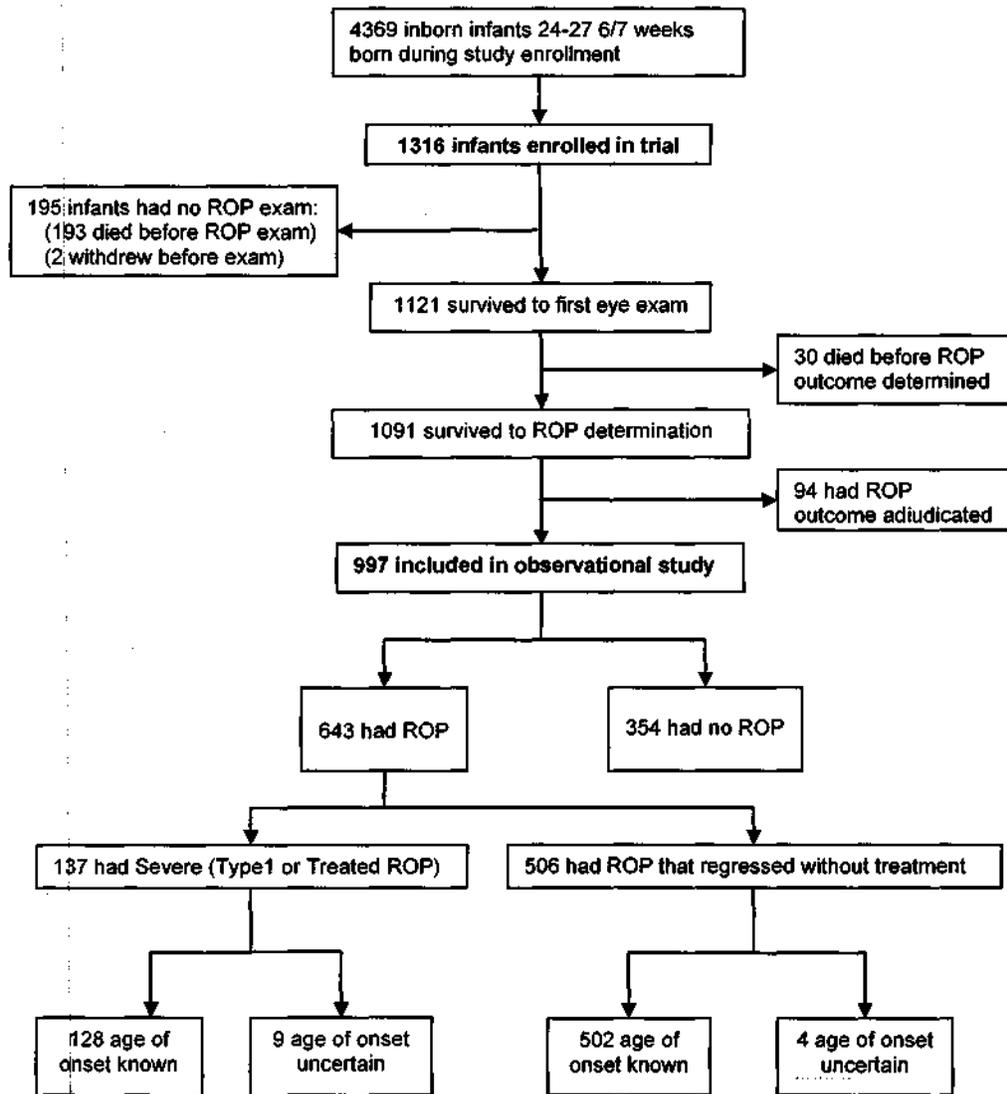
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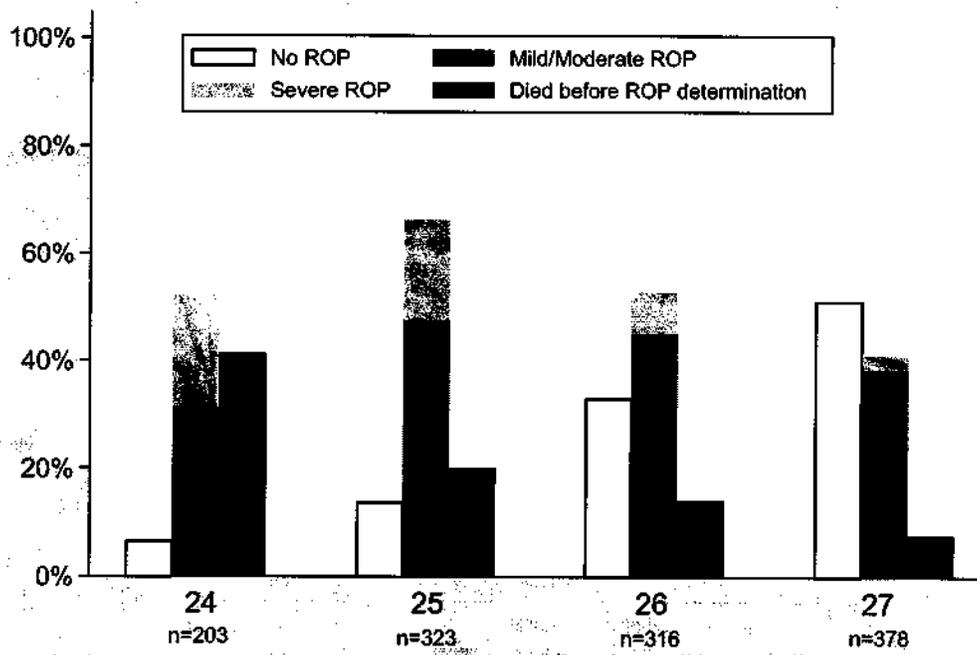
Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

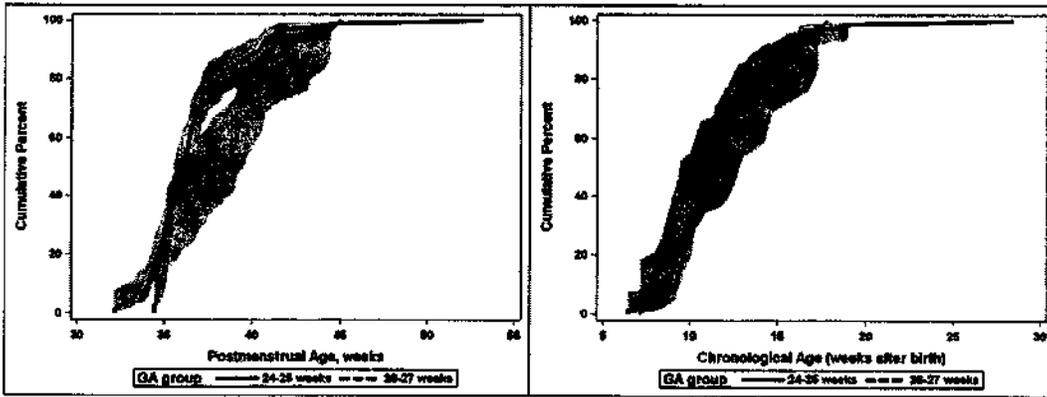
Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.







**From:** Luc Brion  
**To:** Wrage, Lisa Ann  
**Cc:** Das, Abhik (adas@rti.org); Higgins, Rosemary (NIH/NICHD) (E: (b)(6) @gmail.com)  
**Subject:** RE: Jackie LeVan's paper  
**Date:** Friday, October 18, 2013 3:46:23 PM  
**Attachments:** Responses to reviewers 101813.docx  
Jackie LeVan Manuscript NRN 10-18-13.docx

---

Lisa:

Thanks a lot for your help.

I edited the response to reviewers and the text of the manuscript.

In figure 1, the main difference is the % of outborn patients, this does not bias the results since we only used inborn patients in SUPPORT and in this cohort study.

Would you please respond to the 5 remaining queries which I have highlighted with yellow background?

Thanks a lot and best regards,

Luc

---

**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Friday, October 18, 2013 11:03 AM  
**To:** Luc Brion  
**Subject:** RE: Jackie LeVan's paper

Hi Luc,

I am glad your presentation went well.

I've attached your updated figure with a couple of comments included.

Please let me know if you have questions.

Thanks.

Lisa

---

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
**Sent:** Thursday, October 17, 2013 4:17 PM  
**To:** Wrage, Lisa Ann  
**Subject:** Re: Jackie LeVan's paper

Thanks a lot.

I was told the presentation went well.

Luc

Sent from my iPhone

On Oct 17, 2013, at 2:01 PM, "Wrage, Lisa Ann" <wrage@rti.org> wrote:

Hi Luc,

I hope your presentation went well. Yes, I will work on Figure 1, I have another paper submission-related 'deadline' tomorrow and once I've met that I'll work on that figure.

Thanks.

Lisa

---

**From:** Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
**Sent:** Thursday, October 17, 2013 1:44 PM  
**To:** Wrage, Lisa Ann  
**Subject:** Jackie LeVan's paper

Lisa:

I have presented the reviewers' comments and potential additional analyses.  
I attach the revised proposed response to reviewers, in which I trimmed requests to you to a minimum.

Could you please complete figure 1? I would appreciate it.

Rose will look at this and will give additional suggestions.

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1,4</sup> Roy Heyne, MD,<sup>1</sup>  
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Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

**Affiliations:** <sup>1</sup>Department of Pediatrics, University of Texas Southwestern, Dallas, TX; <sup>2</sup>Current affiliation: Pediatrix Medical Group, San Antonio, TX; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>4</sup>Current affiliation: The Ohio State University - Nationwide Children's Hospital; <sup>5</sup>Division of Neonatology, University of California, San Diego, CA; <sup>6</sup>Division of Neonatology, University of Alabama, Birmingham, AL; <sup>7</sup>Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; <sup>8</sup>Eunice Kennedy Shriver National Institute of Child, Health and Human Development, Bethesda, MD

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No reprints needed

**First draft:** Dr LeVan wrote the first draft of the manuscript.

**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

**Funding source:** NICHD

**Financial Statement:** No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

**Conflict of Interest Statement:** There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

**Clinical Trial registration:** NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 197250 words  
Article length: 2,410,697 words  
Revised 10/10/2013

List of Abbreviations:

**ARR**, Absolute risk reduction;

**BPD**, bronchopulmonary dysplasia;

**CI**, confidence interval;

**CPAP**, continuous positive airway pressure;

**DR**, delivery room;

**ETI**, Endotracheal Intubation;

**GA**, gestational age;

**GDB**, generic database;

**NRN**, Neonatal Research Network;

**PDA**, patent ductus arteriosus;

**PMA**, postmenstrual age;

**ROP**, retinopathy of prematurity;

**RR**, relative risk;

**SUPPORT**, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## Abstract

### Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased by 15% after compare medical care practices and neonatal outcomes before and after publication of SUPPORT within NICUs in NRN centers.

### Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. ~~The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.~~

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ~~ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)~~

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

Conclusions:

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

**Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if ~~publication of SUPPORT was temporally associated with changes in clinical practice~~, specifically in the proportion of preterm inborn infants intubated in the DR, decreased changed after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a 15% decrease lower proportion of in ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT, using a conservative estimate based on preliminary data at Parkland Memorial Hospital. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm -infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. The most important neonatal outcomes were se included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes changed after SUPPORT.

## Methods

### Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the

SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT

Trial. The GDB has defined variables with detailed definitions; all patients are followed in GDB to ascertain all listed outcomes. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar ~~but not identical~~ to those used in SUPPORT<sub>5-7</sub><sup>1,2</sup>. Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

The latter criterion was different from SUPPORT, where patients were excluded if a decision had been made to provide full resuscitation for them.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important sSecondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP at discharge, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of

bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): ~~BPD, severe ROP and other ROP outcomes~~, death within 12 hours or by 36 weeks PMA, ~~DR practice outcome~~, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

#### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>46</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and

all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5-137-156</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Sample size analysis:

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%.<sup>14</sup> Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a 15% relative risk reduction in ETI from 80% to 68% with an alpha error less than 5% and a power greater than 99%, even if more than 50% of the patients met exclusion criteria. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

## Results

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). ~~Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population included of 3,849 infants:~~

1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 14.

There was more antenatal steroid use (~~89.6% vs. 82.8%, p<0.0001~~), maternal hypertension (~~27.4% vs. 19.9%, p<0.0001~~), maternal diabetes (~~5.4% vs. 2.6%, p<0.0001~~), cesarean section delivery (~~66.3% vs. 62.1%, p=0.0073~~), and less prolonged rupture of membranes (~~24.1% vs. 27.5%, p=0.017~~) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 22). The adjusted risk of DR ETI (~~adjusted RR 0.88, 95% CI 0.85-0.91~~) significantly decreased after ~~publication of~~ SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 22). The adjusted risk of BPD/death (~~adjusted RR 0.94, 95% CI 0.89-0.99~~), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge, (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP<sub>1</sub> (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 22). In contrast, the adjusted risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only, the appendix. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

#### Discussion:

Infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was four times as

large as the ARR in DR ETI observed in very low birth weight infants in the Vermont Oxford Network over a 10-year span between 2000 and 2009 (3.7%; 95% CI 4.2% to 3.3%).<sup>19</sup> The ARR over a 10-year span in the NRN and Vermont Oxford Network was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%). In this study we compared data before SUPPORT with data after SUPPORT and did not thus we were unable to analyze serial changes in whether the decrease in proportion of ETI in each participating centers. The proportion of ETI in each center could have decreased with increasing use of CPAP and experience with teek place at the time of introduction of and increasing experience with T-piece connectors before, during or after participation in ~~conduction~~ of the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation the trial, or after publication of the results of SUPPORT. The proportion of ETI in at Parkland Memorial Hospital, one of the centers participating in SUPPORT, decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010);<sup>17</sup> ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).<sup>16</sup> In one of the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after introduction of bubble CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between We had hypothesized that the change in the proportion in ETI after SUPPORT and would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this

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~~may have resulted from the limited number of centers included in this study and from the narrow range (82-97%) of and from the fact that 9 of the 11 centers had pre-SUPPORT proportions of ETI in 9 of 11 centers that varied within a narrow range of about 82-97%.~~ and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database ~~and of inborn patients~~ which limits incomplete/missing data and information bias, ~~and the use of multivariate analysis to take into account differences in confounding variables between the two periods, the use of inclusion and exclusion criteria that were similar to resembled (though did not exactly match) those used in SUPPORT, and the inclusion of:~~ We were able to analyze center specific changes after SUPPORT as well as changes in the entire sample, because we only used ~~We elected to limit for this study to centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to I:~~

~~because of large inter-institutional differences that have been observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample.~~

~~However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, strict selection criteria, high percentage of exclusions, the limited number of variables included in the GDB, and secular trends, and lack of information in the . Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in the primary outcomes of SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-~~

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enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB on did not include information on individual use of DR CPAP, oxygen saturation targets in the DR or the NICU, or the rationale used for each various practice, s used for each patient in each center. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Since we did not adjust p value for multiple comparisons, secondary and tertiary variables should all be considered as exploratory. Mortality The risk of death before discharge was significantly decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>19</sup> and between 2003 and 2007.<sup>18,19,20</sup> - but it is consistent with a recent review a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-

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2011.<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21,24</sup>

This study was not designed to test whether any change in secondary or tertiary variables were associated with changes in O2 saturation or with the application in practice of evidence from SUPPORT or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies.

We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since serial oxygen saturation measurements were not prospectively collected in the GDB before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Several center-specific practice guidelines and policies may have individual practice may have changed between the two epochs, based on new information on other studies rather than SUPPORT, e.g., antenatal, DR studies on and NICU management and outcomes antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>22-31,29,29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American

~~Academy of Pediatrics and American Heart Association.<sup>300</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies.~~

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors during SUPPORT and with tight oxygen monitoring and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

#### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ~~ROP/death, BPD/death, and death before discharge in~~ for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

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~~Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.~~

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**Acknowledgments:**

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Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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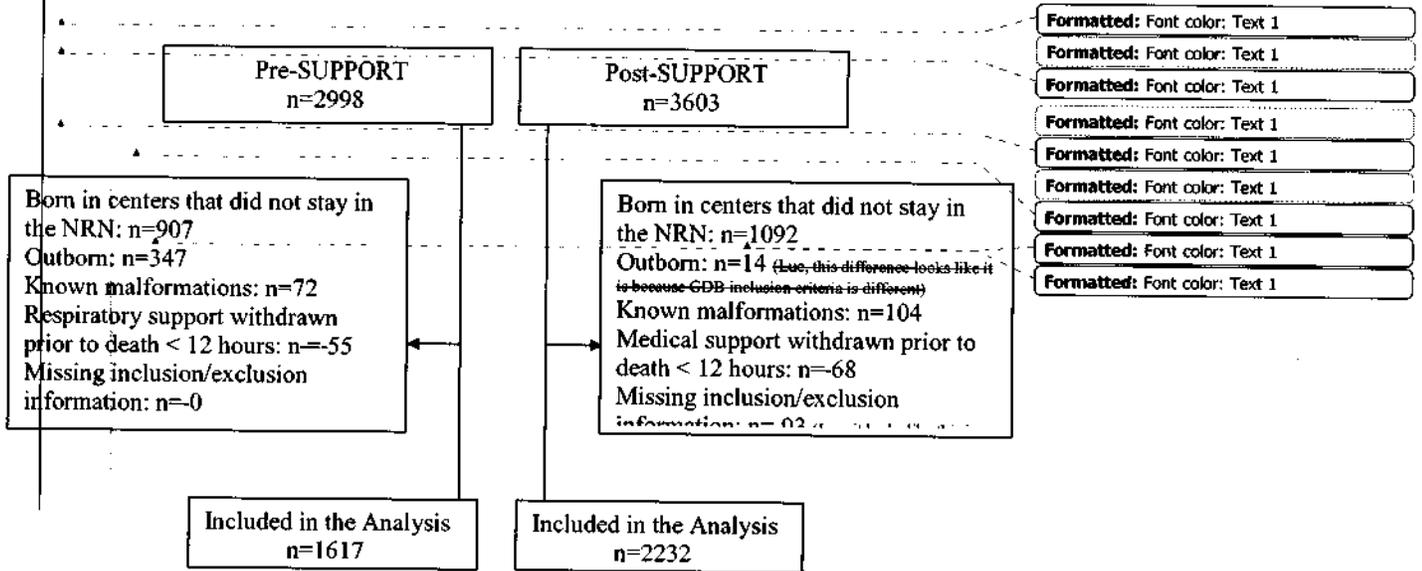
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**Figure Legends**

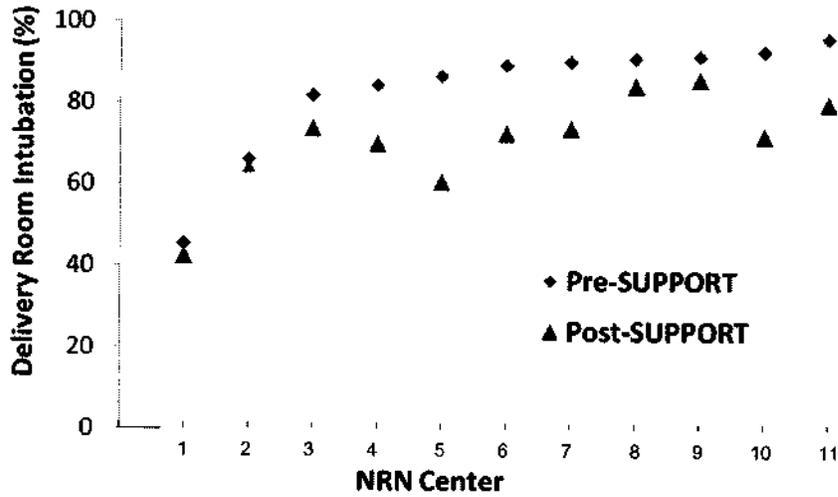
**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

**Figure 1**



**Figure 2**



**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858/1617 (53.1)	1126/2232 (50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727/1617 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603/1617 (37.3)	808/2192 (36.9)	
Hispanic	241/1617 (14.9)	314/2192 (14.3)	
Other	46/1617 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614 (59.1)	1980/2229 (88.8)	<.0001
Multiple birth	370/1617 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004/1617 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322/1617 (19.9)	610/2230 (27.4)	<.0001
Maternal diabetes	42/1617 (2.6)	120/2231 (5.4)	<.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

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Abbreviation: GA, gestational age

<sup>1</sup>presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>4</sup></b>
Intubated in delivery room (primary outcome)	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970/1617 (60.0)	1199/2213 (54.2)	0.0003	:	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	:	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	:	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia (36 weeks)	664/1311 (50.7)	855/1869 (45.8)	0.0064	:	1.04 (0.97-1.1)	0.26
Severe ROP by discharge	174/1294 (13.5)	181/1873 (9.7)	0.0009	:	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306/1617 (18.9)	344/2222 (15.5)	0.0050	:	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	:	0.90 (0.84-0.97)	0.003
Days on ventilator (survivors) until discharge	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 3- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232 (97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup>presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

Ref.: Ms. No. 20131573  
Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members is a separate Appendix file. The figure is at 1000 dpi. We labeled the third table as online only. We include an itemized list of responses to the reviewers.

We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.

*Response: The text of the first version had 2697 words; the revised version has 2410 words. The text of the discussion was shortened by 1/2 page. We have shortened the results section by removing all numbers from the text that were in Figure 1 or in the tables.*

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.jpeds.com/authorinfo>).

*Response: We have shortened the abstract; it contains 197 words. The abstract is structured as indicated.*

Please upload the list of Study Group members as a separate Appendix file.

*Response: the list of Study Group is a separate file.*

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

*Response: Figures are submitted at TIFF files with 1,000 dpi.*

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the

file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

*Response: we have changed online documents as requested.*

Itemized responses to Reviewers:

Reviewer #1: (b)(4), (b)(6)

(b)(4), (b)(6)

Comments:

(b)(4), (b)(5), (b)(6)

Page 0674 of 2000

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(b)(5)

of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** (b)(6)@gmail.com  
**Subject:** Please review - LeVan Paper  
**Date:** Friday, October 18, 2013 1:24:03 AM  
**Attachments:** Jackie LeVan Manuscript NRN 10-17-13.docx  
Responses to reviewers 101713.docx  
s1-In1509858495844769-1939656818Hwf146573536Idv-34176251315098584PDF\_HI0001.pdf

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Rose;

It was great to see you today.

Thanks a lot for your comments. I appreciate your suggestions and your help.

I have revised the proposed response to the reviewers, along what we have discussed today.

I have asked Lisa Wrage to update Figure 1 with information on inclusions for each epoch.

Please let me know if any additional information or data analysis should be added.

Thanks a lot

Best regards,

Luc

Attached:

Submitted manuscript

Proposed revised manuscript

Proposed response to reviewers

---

UT Southwestern Medical Center  
The future of medicine, today.

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1,4</sup> Roy Heyne, MD,<sup>1</sup>  
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Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

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No reprints needed

**First draft:** Dr LeVan wrote the first draft of the manuscript.

**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

**Funding source:** NICHD

**Financial Statement:** No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

**Conflict of Interest Statement:** There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

**Clinical Trial registration:** NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: ~~197250~~ words  
Article length: ~~2,41069774~~ words  
Revised ~~109/108713/13~~

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## Abstract

### Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased by 15% after compare medical care practices and neonatal outcomes before and after publication of SUPPORT withiwithin NICUs in NRN centers.

### Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. ~~The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.~~

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ~~ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)~~

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

**Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if ~~publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR, decreased~~ changed after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a 15% decrease ~~lower proportion of in ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT, using a conservative estimate based on preliminary data at Parkland Memorial Hospital.~~ We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. The most important neonatal outcomes were ~~se included~~ the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. ~~We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes~~ changed after SUPPORT.

## Methods

### Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the

SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. The GDB has defined variables with detailed definitions; all patients are followed in GDB to ascertain all listed outcomes. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar ~~but not identical~~ to those used in SUPPORT<sup>1,2</sup>. however they were not identical because of specific variables and definitions listed in GDB at each period. Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important sSecondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP at discharge, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of

bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

#### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>46</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and

all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5-137-156</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Sample size analysis:

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%.<sup>14</sup> Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a 15% relative risk reduction in ETI from 80% to 68% with an alpha error less than 5% and a power greater than 99%, even if more than 50% of the patients met exclusion criteria. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

## Results

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). ~~Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study, and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population included of 3,849 infants:~~

1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1~~1~~.

There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2~~2~~). The adjusted risk of DR ETI (~~adjusted RR 0.88, 95% CI 0.85-0.91~~) significantly decreased after ~~publication of~~ SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2~~2~~). The adjusted risk of BPD/death (~~adjusted RR 0.94, 95% CI 0.89-0.99~~), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP<sub>1</sub> (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 22). In contrast, the adjusted risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 3; online only, ~~the appendix~~. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

#### **Discussion:**

Infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was four times as

~~large as the ARR in DR ETI observed in very low birth weight infants in the Vermont Oxford Network over a 10-year span between 2000 and 2009 (3.7%; 95% CI 4.2% to 3.3%).<sup>18</sup> The ARR over a 10-year span in the NRN and Vermont Oxford Network was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%). In this study we compared data before SUPPORT with data after SUPPORT and did not thus we were unable to analyze serial changes in whether the decrease in proportion of ETI in each participating centers. The proportion of ETI in each center could have decreased with increasing use of CPAP and experience with teek place at the time of introduction of and increasing experience with T-piece connectors before, during or after participation in -conduction of the Feasibility Trial (which took place in 5 of the 11 centers during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation the trial, or after publication of the results of SUPPORT. The proportion of ETI in at Parkland Memorial Hospital, one of the centers participating in SUPPORT, decreased in non-enrolled patients from baseline before SUPPORT (2003-20054) to epochs during SUPPORT (2005-2009) and before its publication (20096-201009);<sup>17</sup> ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).<sup>16</sup> In one of the 11 NRN centers that participated in SUPPORT, the proportion of ETI decreased after introduction of bubble CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study. Lack of correlation between We had hypothesized that the change in the proportion in ETI after SUPPORT and would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this~~

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~~may have resulted from the limited number of centers included in this study and from the narrow range (82-97%) of and from the fact that 9 of the 11 centers had pre-SUPPORT proportions of ETI in 9 of 11 centers that varied within a narrow range of about 82-97%.~~ and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>48</sup> and between 2003 and 2007.<sup>49</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account ~~differences in confounding variables between the two periods, the use of inclusion and exclusion criteria that were similar to resembled (though did not exactly match)~~ those used in SUPPORT, and the inclusion of ~~We were able to analyze center-specific changes after SUPPORT as well as changes in the entire sample, because we only used~~ ~~We elected to limit for this study to centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to 1- because of Large~~

~~inter-institutional differences that have been observed in previous NRN studies; this allowed us to analyze center specific changes after SUPPORT as well as changes in the entire sample. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center specific changes after SUPPORT as well as changes in the entire sample.~~

However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, strict selection criteria to high percentage of exclusions, the limited number of variables included in the GDB, and secular trends, and lack of information in the. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in the primary outcomes of SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-

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enrolled patients during SUPPORT and before its publication,<sup>24</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB on did not include information on individual use of DR CPAP, oxygen saturation targets in the DR or the NICU, or the rationale used for each various practice, s used for each patient in each center. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.

Since we did not adjust p value for multiple comparisons, secondary and tertiary variables should all be considered as exploratory. Mortality The risk of death before discharge was significantly decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>19</sup> and between 2003 and 2007,<sup>18,19,20</sup> but it is consistent with a recent review a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-

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2011.<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21,24</sup>

This study was not designed to test whether any change in secondary or tertiary variables were associated with changes in O2 saturation or with the application in practice of evidence from SUPPORT or other studies. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies.

We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since serial oxygen saturation measurements were not prospectively collected in the GDB before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Several center-specific practice guidelines and policies may have changed between the two epochs, based on new information on other studies rather than SUPPORT, e.g., antenatal, DR studies on and NICU management and outcomes antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>22-31,29,29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American

~~Academy of Pediatrics and American Heart Association.<sup>300</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies.~~

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors during SUPPORT and with tight oxygen monitoring and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

#### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ~~ROP/death, BPD/death, and death before discharge in~~ for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial

compared to a period before SUPPORT. ~~The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.~~

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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**Jaclyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Wayne State University, University of Michigan, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; John Barks, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN, Geraldine Muran, RN BSN.

The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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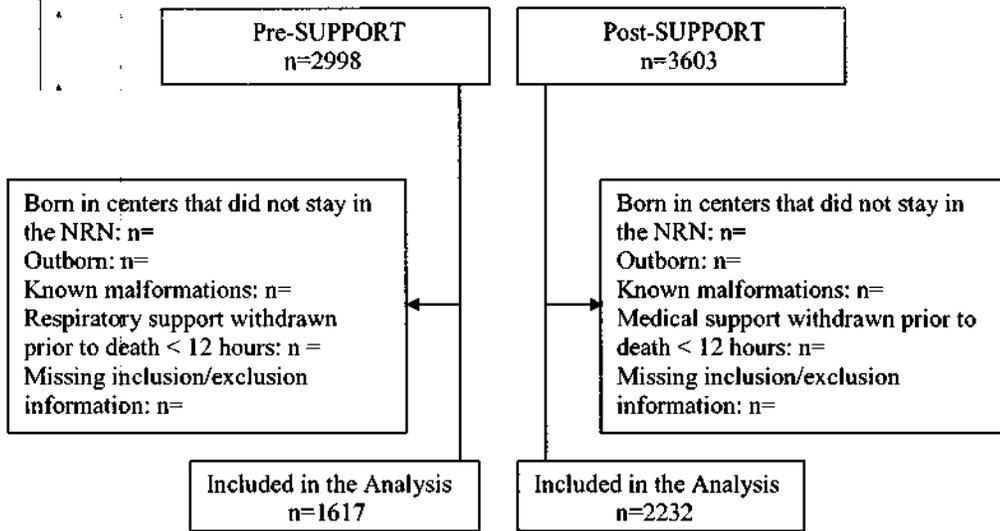
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## Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

**-Figure 1**

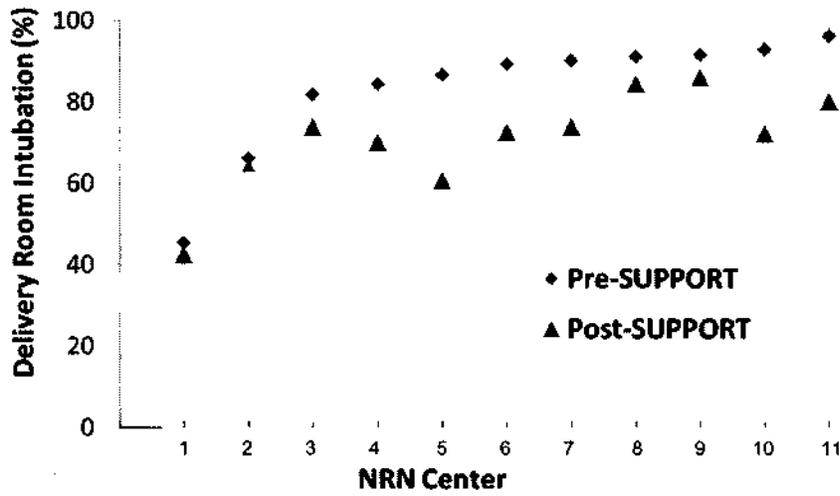


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**Figure 2**

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**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
<b>Birth weight (grams)</b>	<b>825 (191)</b>	<b>818 (194)</b>	<b>0.32</b>
<b>GA (weeks)</b>	<b>25.7 (1.1)</b>	<b>25.7 (1.1)</b>	<b>0.93</b>
<b>Male</b>	<b>858/1617 (53.1)</b>	<b>1126/2232 (50.5)</b>	<b>0.11</b>
<b>Race/ethnicity:</b>			
<b>Non Hispanic Black</b>	<b>727/1617 (45.0)</b>	<b>965/2192 (44.0)</b>	<b>0.02</b>
<b>Non Hispanic White</b>	<b>603/1617 (37.3)</b>	<b>808/2192 (36.9)</b>	
<b>Hispanic</b>	<b>241/1617 (14.9)</b>	<b>314/2192 (14.3)</b>	
<b>Other</b>	<b>46/1617 (2.8)</b>	<b>105/2192 (4.8)</b>	
<b>Antenatal Steroids: any type</b>	<b>1338/1616 (82.8)</b>	<b>1994/2225 (89.6)</b>	<b>&lt;.0001</b>
<b>Antenatal Steroids: betamethasone</b>	<b>953/1614 (59.1)</b>	<b>1980/2229 (88.8)</b>	<b>&lt;.0001</b>
<b>Multiple birth</b>	<b>370/1617 (22.9)</b>	<b>540/2228 (24.2)</b>	<b>0.33</b>
<b>Mode of delivery: cesarean section</b>	<b>1004/1617 (62.1)</b>	<b>1476/2228 (66.3)</b>	<b>0.008</b>
<b>Prolonged rupture of membranes: (&gt; 24 hours)</b>	<b>436/1586 (27.5)</b>	<b>520/2161 (24.1)</b>	<b>0.017</b>
<b>Maternal hypertension</b>	<b>322/1617 (19.9)</b>	<b>610/2230 (27.4)</b>	<b>&lt;.0001</b>
<b>Maternal diabetes</b>	<b>42/1617 (2.6)</b>	<b>120/2231 (5.4)</b>	<b>&lt;.0001</b>
<b>Maternal Antibiotics</b>	<b>1198/1615 (74.2)</b>	<b>1618/2228 (72.6)</b>	<b>0.28</b>

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Abbreviation: GA, gestational age

<sup>1</sup>presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>4</sup></b>
<b>Intubated in delivery room (primary outcome)</b>	1313/1617 (81.2)	1539/2232 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
<b>BPD or death at 36 weeks</b>	970/1617 (60.0)	1199/2213 (54.2)	0.0003	:	0.94 (0.89-0.99)	0.02
<b>Severe ROP or death</b>	515/1581 (32.6)	559/2165 (25.8)	<0.0001	:	0.81 (0.73-0.89)	<0.0001
<b>Death before discharge</b>	358/1614 (22.2)	393/2196 (17.9)	0.001	:	0.86 (0.76-0.98)	0.02
<b>Bronchopulmonary dysplasia (36 weeks)</b>	664/1311 (50.7)	855/1869 (45.8)	0.0064	:	1.04 (0.97-1.1)	0.26
<b>Severe ROP by discharge</b>	174/1294 (13.5)	181/1873 (9.7)	0.0009	:	0.63 (0.52-0.77)	<0.0001
<b>Death by 36 weeks</b>	306/1617 (18.9)	344/2222 (15.5)	0.0050	:	0.88 (0.76-1.00)	0.06
<b>Death or mechanical ventilation on day 7</b>	741/1613 (45.9)	875/2211 (39.6)	<0.0001	:	0.90 (0.84-0.97)	0.003
<b>Days on ventilator (survivors) until discharge</b>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FIO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 3- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup>presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

Ref.: Ms. No. 20131573

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members is a separate Appendix file. The figure is at 1000 dpi. We labeled the third table as online only. We include an itemized list of responses to the reviewers.

We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.

*Response: The text of the first version had 2697 words; the revised version has 2410 words. The text of the discussion was shortened by ½ page. We have shortened the results section by removing all numbers from the text that were in Figure 1 or in the tables.*

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.jpeds.com/authorinfo>).

*Response: We have shortened the abstract; it contains 197 words. The abstract is structured as indicated.*

Please upload the list of Study Group members as a separate Appendix file.

*Response: the list of Study Group is a separate file.*

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

*Response: Figures are submitted at TIFF files with 1,000 dpi.*

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the

file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

*Response: we have changed online documents as requested.*

**Itemized responses to Reviewers:**

**Reviewer #1:** (b)(4),(b)(5),(b)(6)

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# PEDIATRICS

## **Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

Journal:	<i>Pediatrics</i>
Manuscript ID:	Draft
Article Type:	Regular Article
Date Submitted by the Author:	n/a
Complete List of Authors:	LeVan, Jaelyn; <i>Pediatrics</i> Medical Group, <i>Pediatrics</i> Brion, Luc; UT Southwestern Medical Center at Dallas, <i>Pediatrics</i> ; Wrage, Lisa; Research Triangle Institute, Statistics Research Division Gantz, Marie; RTI International, Statistics and Epidemiology Unit Wyckoff, Myra; UT Southwestern Medical Center, <i>Pediatrics</i> Sanchez, Pablo; UT Southwestern Medical Center, <i>Pediatrics</i> Heyne, Roy; University of Texas Southwestern Medical Center, Department of <i>Pediatrics</i> / Division of Neonatal-Perinatal Medicine Jaleel, Mambambath; University of Texas Southwestern Medical Center, Department of <i>Pediatrics</i> / Division of Neonatal-Perinatal Medicine Finer, Neil; UCSD Medical Center, Neonatology Carlo, Waldemar; University of Alabama at Birmingham, Division of Neonatology Das, Abhik; RTI International, Statistics and Epidemiology Stoll, Barbara; Emory University, Department of <i>Pediatrics</i> , Higgins, Rosemary; Eunice Kennedy Shriver National Institute of child health and human development, Pregnancy and perinatology branch
Keyword/Category:	Gestational age, Tracheal tube, Preterm infants, Mortality rates, cohort studies

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Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous  
positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age;  
GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN,  
Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP,  
retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and  
Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia,  
retinopathy of prematurity, mortality

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Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and  
Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure  
(CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm  
infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in  
NICHD centers that participated.

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**Contributors' Statement Page**

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Rose Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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3 **Abstract**  
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6 **Introduction**

7 The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which  
8 preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) CPAP  
9 initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen  
10 saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to  
11 compare medical care practices and neonatal outcomes before and after the publication of  
12 SUPPORT within the NICUs in the NRN centers.  
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15 **Methods:**

16 This was a retrospective cohort study using the prospective NRN generic database. We  
17 included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-  
18 12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11.  
19 We excluded infants with syndromes or major malformations and those who received  
20 only comfort care. The primary outcome was DR intubation. The most important  
21 secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe  
22 retinopathy of prematurity (ROP)/death and death by discharge.  
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26 **Results:**

27 After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR  
28 intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI  
29 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge  
30 (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.  
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33 **Conclusions:**

34 After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating  
35 NRN Centers after publication of SUPPORT had significantly lower percentages of DR  
36 intubation, BPD/death, ROP/death and death at discharge compared to infants born  
37 before SUPPORT.  
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4 **Introduction:**  
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6 The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant,  
7 Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter  
8 randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks  
9 gestational age (GA) were randomized at birth to (1) either continuous positive airway  
10 pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited  
11 ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant  
12 administration (within one hour of birth) followed by a conventional ventilation strategy,  
13 and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February  
14 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA  
15 stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup>  
16 weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of  
17 the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD])  
18 were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the  
19 CPAP group, infants had a lower proportion of endotracheal intubation or postnatal  
20 steroids for BPD, had fewer days of mechanical ventilation among survivors, and were  
21 more likely to be alive and off mechanical ventilation by day seven. Among infants with  
22 GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks  
23 was significantly lower in the CPAP group than in the surfactant group. There was also  
24 less use of epinephrine in the DR in the CPAP group than in the surfactant group. The  
25 risk of the primary outcome of the saturation target trial (severe retinopathy of  
26 prematurity [ROP] or death) was not significantly different between the two oxygen  
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3 saturation target groups. However, the risk of death was higher and that of severe ROP  
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5 was lower in the low saturation target group than in the high target group.  
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8 The objective of this study was to determine if publication of SUPPORT was temporally  
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10 associated with changes in clinical practice, specifically in the proportion of preterm  
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12 inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be  
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14 a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to  
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16 the period before SUPPORT. We speculated that the decrease in proportion of ETI in the  
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18 DR in each center after SUPPORT would depend on the baseline proportion before the  
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20 trial. In this study we also aimed to determine whether neonatal outcomes in preterm  
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22 infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included  
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24 the composite of death or BPD, the composite of severe ROP or death before discharge  
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26 from the hospital, and death before discharge. We also examined if publication of  
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28 SUPPORT was followed by changes in several other neonatal processes of care and  
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30 outcomes.  
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### 39 Methods

#### 40 Study Design

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42 This was a retrospective birth cohort analysis with before/after design. We extracted data  
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44 from the NICHD Generic Database (GDB) (a registry of very low birth weight infants  
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46 born alive in NRN centers) in one birth cohort of patients born before the initiation of the  
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48 SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT  
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50 Trial. We included the eleven centers that participated in the SUPPORT trial and in the  
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52 NRN during the cycles relevant to the two cohorts.  
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Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variable:

The primary outcome variable was ETI in DR.

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4 Secondary outcome variables:

5 The most important secondary outcomes included the composite of death or BPD  
6 (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP  
7 (defined as ROP surgery or retinal detachment) or death before discharge from the  
8 hospital, and death before discharge. The definitions of BPD and ROP for this study were  
9 based on those used in the GDB; they were similar but not identical to the primary  
10 outcome of the SUPPORT trial.  
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13 Other secondary outcomes included BPD, severe ROP and other ROP outcomes, death  
14 within 12 hours or by 36 weeks PMA, surfactant use, DR outcome, Apgar scores,  
15 temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis,  
16 intraventricular hemorrhage (IVH), oxygen supplementation, ventilation and CPAP use,  
17 patent ductus arteriosus, feeding and weight related variables, proven necrotizing  
18 enterocolitis (NEC) (stage II or greater, modified Bell's classification)<sup>5</sup> and length of  
19 hospital stay among survivors.  
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39 Statistical analysis

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41 Variables of interest were compared by study group using chi-square tests for categorical  
42 variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student  
43 t-tests for all other continuous variables. Robust Poisson regression models were used for  
44 dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence  
45 intervals (CI). General linear models were used for continuous outcomes, to obtain  
46 differences in means and 95% CI. All models included pre-specified prenatal covariates  
47 (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal  
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3 corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well  
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5 as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the  
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7 unadjusted tests, and that preceded the outcome. The models for primary outcome and all  
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9 secondary outcomes, with the exception of BPD, included additional variables that  
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11 preceded birth (race/ethnicity, cesarean section, rupture of membranes  $> 24$  hours,  
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13 maternal hypertension, and maternal diabetes), but not postnatal variables to which some  
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15 infants may not have been exposed before the outcome took place. The model for BPD  
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17 contained these same additional variables as well as intubation in the DR, surfactant,  
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19 FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment,  
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21 late onset sepsis and intrauterine growth restriction.<sup>7-16</sup> Since we did not adjust p value  
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23 for multiple comparisons, all secondary analyses should be considered as exploratory.  
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29 A Spearman correlation was used to assess whether the change in proportion of delivery  
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31 room intubations from the first period (pre-SUPPORT) to the second period (post-  
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33 SUPPORT) was higher in centers with higher proportion of intubation during the first  
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35 period.  
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## 41 **Results**

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43 A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age were born during the study  
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45 periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1).  
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48 Of these, 1,999 infants were born in NRN centers not included in this study and an  
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50 additional 361 were outborn, these infants were excluded. Of the remaining infants, 176  
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52 infants with known malformations, 123 infants who had respiratory or medical support  
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54 withdrawn prior to death  $< 12$  hours, and 93 infants who had missing inclusion/exclusion  
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3 information were excluded, leaving a total study population of 3,849 infants: 1,617

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5 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

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8 The baseline maternal and neonatal characteristics of both groups are shown in Table 1.

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10 There was more antenatal steroid use (89.6% vs. 82.8%,  $p<0.0001$ ), maternal

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12 hypertension (27.4% vs. 19.9%,  $p<0.0001$ ), maternal diabetes (5.4% vs. 2.6%,

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14  $p<0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p=0.0078$ ), and prolonged

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16 rupture of membranes (24.1% vs. 27.5%,  $p=0.017$ ) in the post-SUPPORT group, and

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18 race/ethnic distribution was different from the pre-SUPPORT group.

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20 For the primary outcome, unadjusted comparison showed a significant decrease in the

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22 proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR

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24 ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of

25  
26 SUPPORT.

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28 For the most important secondary outcomes, unadjusted comparison showed a significant

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30 decrease in the proportion of death or BPD, death or ROP, and death in the post-

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32 SUPPORT group (Table 3). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI

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34 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before

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36 discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication

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38 of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77)

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40 and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI

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42 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast,

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44 the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted

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46 RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average

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4 number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after  
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6 SUPPORT.

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8 Additional unadjusted comparisons are shown in table 4. Several differences were  
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10 observed between the two periods.

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12 Figure 2 shows the proportion of infants intubated in the DR during the first and second  
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14 study periods in all centers in the study. The correlation between the proportion of  
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16 intubations in the DR during the first period and the change in proportion of intubations  
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18 in the DR from the first to the second period was not significant (Spearman correlation  
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20 coefficient -0.44, p=0.18).  
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27 **Discussion:**

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29 Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers  
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31 participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and  
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33 ROP or death compared to those infants born before the initiation of the SUPPORT.  
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35 Severe ROP and death or mechanical ventilation at day of life 7 were significantly  
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37 decreased in the group of infants in the post-SUPPORT group. These findings contrast  
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39 with previous published reports from the NICHD NRN, which failed to show any  
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41 improvement in survival without major neonatal morbidity between 1995-96 and 1997-  
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43 2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths  
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45 among extremely low birthweight infants enrolled in the GDB which showed a decrease  
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47 in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results  
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49 of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study  
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3 sites. These findings also support the significant impact that the results of a randomized  
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5 controlled trial have on clinical practice management and patient outcomes.  
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8 The strengths of this study include a large sample size, the use of a prospective database  
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10 which limits incomplete/missing data and information bias, and the use of multivariate  
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12 analysis to take into account differences in confounding variables between the two  
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14 periods. Limitations of this study include the observational design, which introduces  
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16 confounding variables and bias and prevents any cause-effect interpretation, and the  
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18 before/after study design, which could introduce changes in patient population, and  
19  
20 secular trends. In this study we compared data before SUPPORT with data after  
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22 SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI  
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24 already started during SUPPORT or occurred after its publication. The proportion of ETI  
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26 at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and  
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28 before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the  
29  
30 Vermont Oxford Neonatal Network. Since the current study includes several outcome  
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32 variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p  
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34 values are presented for informational purposes. These analyses should be considered as  
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36 exploratory. It is possible that additional unknown biases or confounding variables, such  
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38 as changes in personnel, could have affected the results. Some centers may have changed  
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40 practice guidelines and providers may have changed their practice based on SUPPORT.  
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42 Since oxygen saturation was not prospectively collected before and after SUPPORT, it is  
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44 impossible to determine whether changes in severe ROP and changes in mortality after  
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46 SUPPORT reported in the present study are related to changes in median or ranges of  
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48 oxygen saturation. Center-specific practice guidelines and individual practice may have  
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3 changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and  
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5 prophylaxis of patent ductus arteriosus,<sup>23-25</sup> synchronized nasal intermittent positive-  
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7 pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or  
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9 nutrition.<sup>29</sup> DR practices, including oxygen exposure and thermoregulation, may have  
10  
11 changed based on new resuscitation literature and on the revised 2010 national  
12  
13 resuscitation program of the American Academy of Pediatrics and American Heart  
14  
15 Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or  
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17 approach to diagnosis and treatment of patent ductus arteriosus may have changed based  
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19 on results of other studies.  
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#### 25 26 27 Conclusion

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29 After adjustment for baseline variables, the proportion of DR ETI, ROP/death,  
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31 BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born  
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33 at Network Centers was lower following the publication of SUPPORT trial compared to a  
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35 period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical  
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37 ventilation at day of life seven also was significantly lower. In contrast, the risk of death  
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39 at 36 weeks PMA and of BPD did not change significantly. The average number of  
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41 ventilator days among survivors was lower after SUPPORT.  
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46 Since this is an observational study, it is impossible to determine the relative contribution  
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48 of the results of SUPPORT trial and other studies on changes in clinical practice and  
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50 patient outcomes at NRN study sites. However, our findings support the potential impact  
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52 that the results of a randomized controlled trial may have on clinical practice  
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54 management and patient outcomes.  
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The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; University of Texas Southwestern Medical Center; University of Texas Health Science Center at Houston; Wayne State University; Stanford University; University of Alabama at Birmingham.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013. E-PAS2013:2924.474

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**Figure Legends**

**Figure 1. Flow diagram**

**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

Table 1. Maternal and Neonatal Characteristics<sup>1</sup>

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

Table 2. Primary Outcome<sup>1</sup>

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Adjusted RR <sup>3</sup> (95% CI)	Adjusted p-value <sup>3</sup>
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001

Abbreviation: RR, relative risk

<sup>1</sup> presented as n (%)

<sup>2</sup> unadjusted p-value from Chi-Square tests

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

<sup>4</sup> adjusted p-values from robust Poisson model

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Table 3. Secondary Outcomes<sup>1</sup>

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Difference in Means <sup>3</sup> (95% CI)	adjusted RR <sup>3</sup> (95% CI)	Adjusted p value <sup>4</sup>
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors) <sup>4</sup>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 4. Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

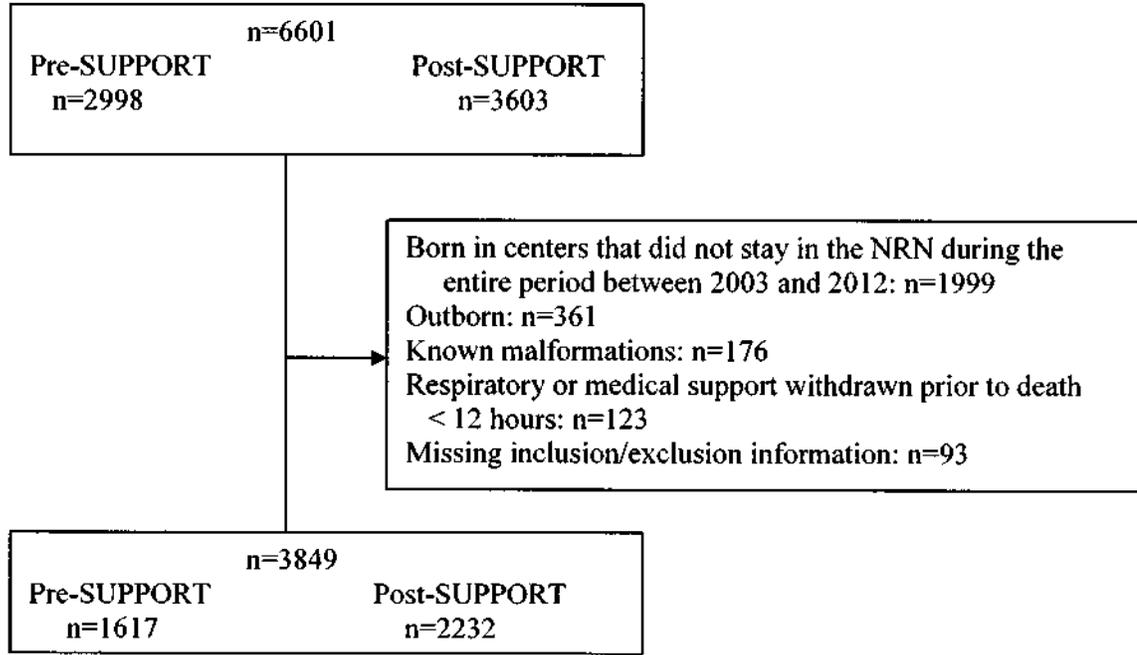
<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

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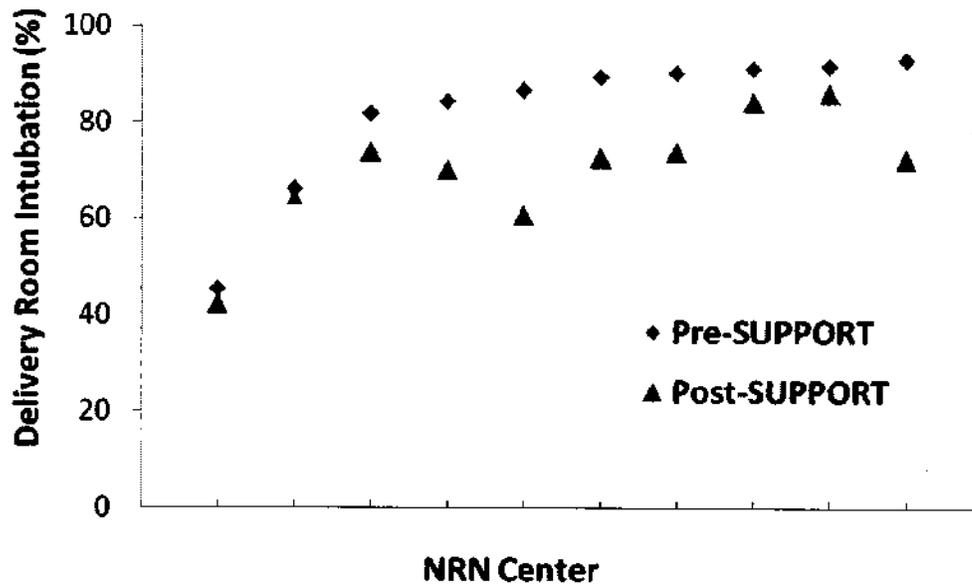
Figure 1



**Confidential - Not for Circulation**

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Figure 2



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies  
**Date:** Thursday, October 17, 2013 1:46:54 PM

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I haven't had time to update - will do it later

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 17, 2013 1:35 PM  
**To:** 'Reardon, Sara'  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies

All our voice mails say that. Thanks for reminding me—I need to update mine as well.

**From:** Reardon, Sara [mailto:Sara.Reardon@us.nature.com]  
**Sent:** Thursday, October 17, 2013 1:35 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies

Ok thanks! Her voicemail had said she was furloughed so I wasn't sure if that meant the study was delayed. Thanks for getting back

Sara

**From:** Bock, Robert (NIH/NICHD) [E] [mailto:bockr@exchange.nih.gov]  
**Sent:** Thursday, October 17, 2013 12:54 PM  
**To:** Reardon, Sara  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Interview with Nature on preemie studies

Hi Sara.

Dr. Higgins is tied up in meetings today and asked me to get back to you. During the shutdown, a statement was sent to reporters, explaining that NIH had notified grantees with existing grants could draw down on their grant funds. If you need a copy, I can get one for you.

The short answer to your question, however, is that none of the studies you asked about were delayed--the research was supported with cooperative agreements, funding for which was awarded in April 1, 2013, for work to be conducted through March 31, 2014.

I hope this is helpful. Please let us know if you need anything else.

Bob Bock  
Press Officer  
NICHD

**From:** Reardon, Sara [Sara.Reardon@us.nature.com]

**Sent:** Thursday, October 17, 2013 11:35 AM

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

**Subject:** Interview with Nature on preemie studies

Dear Dr. Higgins,

I'm a reporter at Nature and am writing about the aftereffects of the NIH shutdown. I was going through [Clinicaltrials.gov](http://Clinicaltrials.gov) and saw that you had several interventional studies on preemies that were due to start up in the next couple of months. Would you have a few minutes to talk about whether the shutdown has affected these trials getting off the ground? Please let me know if there would be a convenient way to reach you.

Thank you, I look forward to hearing from you!

Sara

Sara Reardon

Reporter, Nature

968 National Press Building

529 14<sup>th</sup> St NW

Washington, DC 20045

Office: 202-626-2514

Cell: (b)(6)

Twitter: @sara\_reardon

[www.nature.com/news](http://www.nature.com/news)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies  
**Date:** Thursday, October 17, 2013 12:38:40 PM

---

Sure- I am (b)(5)

Thanks  
Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 17, 2013 12:27 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** FW: Interview with Nature on preemie studies

Hi Rose. This reporter was in touch with Renate earlier. I'm thinking of (b)(5)

(b)(5)

Is that OK with you?

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, October 17, 2013 12:22 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Fine, Amanda (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies

Thanks, Bob. Welcome back to you all! Yes, we worked with Sara during the shutdown and provided her with the statement that says grantees with existing grants could continue to draw down their funds during the shutdown so their studies were not affected. It would be good if you can (b)(5)

(b)(5)

Best,  
Renate

**NIH Statement on the Effect of Government Shutdown as of October 10, 2013**

NIH has notified grantees (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-126.html>) that it will not take any actions on grant applications or awards during a government shutdown. HHS is, however, continuing to operate the Payment Management System so that grantees with existing grants with no restrictions can continue to draw down their grant funds. This includes funding for clinical trials conducted by grantee organizations. Additionally, the Grants.gov system is operational and accepting

grant applications, which are being stored but not processed. NIH is not available to provide programmatic services to grantees during a shutdown.

The HHS staffing during shutdown includes numbers for NIH:

[http://www.hhs.gov/budget/fy2014/fy2014contingency\\_staffing\\_plan-rev2.pdf](http://www.hhs.gov/budget/fy2014/fy2014contingency_staffing_plan-rev2.pdf). On October 1, NIH furloughed 13,698 (73 percent) of its total 18,646 employees and retained 4,948 (32 percent) for the safety of human life or the protection of property.

NIH activities that **will continue under a shutdown**:

- Patient care for current NIH Clinical Center patients
- Ongoing protocols at the NIH Clinical Center
- Animal care services to protect the health of NIH animals
- NIH facilities services including at the NIH power plant
- NIH police and guard services
- NIH fire department services
- NIH IT services to ensure information security and support excepted activities, e.g. PubMed

NIH activities that **cease under a shutdown**:

- All NIH grant review, awards and program management
- The admission of new patients at the NIH Clinical Center (unless deemed medically necessary by the NIH Clinical Center Director)
- Initiation of new protocols at the NIH Clinical Center
- Basic research conducted by NIH scientists
- Translational research conducted by NIH scientists that develops clinical applications of scientific knowledge
- Training of graduate students and postdoctoral fellows at NIH facilities
- Scientific meetings at NIH facilities
- Travel of NIH scientists to scientific meetings
- Some NIH veterinary services
- NIH scientific equipment services
- Almost all NIH administrative functions
- NIH childcare center services
- NIH mail, cafeterias, and most visitor services

#### **Status of clinical research protocols at the NIH Clinical Center during the shut down**

During the government shutdown, the NIH Clinical Center will assure the care of patients already enrolled in the 1,437 clinical studies now under way. NIH is not enrolling new patients in studies, except in cases where all of the following criteria are met:

- 1) The patient's illness is imminently life threatening.
- 2) The patient meets the eligibility criteria for an existing protocol.
- 3) The protocol offers some hope for an improved outcome.

A team of doctors at the NIH Clinical Center is determining on a case-by-case basis when a patient meets the above criteria. Between October 1-8, the NIH Clinical Center enrolled 12 patients with life threatening conditions. Under normal circumstances, approximately 200 new patients are enrolled per week, approximately 15% of those are children, and approximately 33% of those children have cancer.

With significantly reduced staff as a result of furloughs from the government shutdown, the NIH Clinical Center must remain focused on assuring the care of patients already enrolled in its clinical studies.

No new studies will be started during a shutdown. The opening of seven new protocols at the NIH Clinical Center has been deferred as of Oct. 9, 2013.

Please note that this information applies to trials conducted at the NIH Clinical Center, not at outside organizations that receive funds from NIH to run trials at their institutions.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 17, 2013 12:17 PM  
**To:** Myles, Renate (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** FW: Interview with Nature on preemie studies

Welcome back!

Please see below, from a reporter working on a story about how the shutdown has affected research.

The short answer to her question is that these studies operate under a cooperative agreement which was funded last April, and so were unaffected by the shutdown. (I don't know whether or not the (b)(5) [redacted])

My thinking is that either (b)(5) [redacted]

(b)(5) [redacted]

Please let me know.

Thanks.  
Bob

---

**From:** Reardon, Sara [Sara.Reardon@us.nature.com]  
**Sent:** Thursday, October 17, 2013 11:35 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Interview with Nature on preemie studies

Dear Dr. Higgins,

I'm a reporter at Nature and am writing about the aftereffects of the NIH shutdown. I was going through Clinicaltrials.gov and saw that you had several interventional studies on preemies that were due to start up in the next couple of months. Would you have a few minutes to talk about whether the shutdown has affected these trials getting off the ground? Please let me know if there would be a convenient way to reach you.

Thank you, I look forward to hearing from you!

Sara

Sara Reardon

Reporter, Nature  
968 National Press Building  
529 14<sup>th</sup> St NW  
Washington, DC 20045  
Office: 202-626-2514  
Cell: (b)(6)  
Twitter: @sara\_reardon  
[www.nature.com/news](http://www.nature.com/news)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Raju, Tonse (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies  
**Date:** Thursday, October 17, 2013 11:43:05 AM

---

None of the studies were delayed -the sites and DCC are funded via cooperative agreements and their funds were awarded April 1, 2013 for work to be conducted through March 31, 2014. The sequester did result in a slight drop in their funding (5-6%).

My concern is (b)(5)

(b)(5)

Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, October 17, 2013 11:39 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Raju, Tonse (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Interview with Nature on preemie studies

OK. I will definitely check with Renate. Before I do, let me ask, were you indeed forced to delay the beginning of these studies because of the shutdown?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, October 17, 2013 11:37 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Raju, Tonse (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** FW: Interview with Nature on preemie studies

Bob -

Can you get some guidance for me on this request? I have my out of office on as I am a at steering committee meeting today and tomorrow.

Thanks  
Rose

---

**From:** Reardon, Sara [Sara.Reardon@us.nature.com]  
**Sent:** Thursday, October 17, 2013 11:35 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Interview with Nature on preemie studies

Dear Dr. Higgins,

I'm a reporter at Nature and am writing about the aftereffects of the NIH shutdown. I was going through Clinicaltrials.gov and saw that you had several interventional studies on preemies that were due to start up in the next couple of months. Would you have a few minutes to talk about whether the shutdown has affected these trials getting off the ground? Please let me know if there would be a convenient way to reach you.

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Sara Reardon  
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529 14<sup>th</sup> St NW  
Washington, DC 20045  
Office: 202-626-2514  
Cell: (b)(6)  
Twitter: @sara\_reardon  
[www.nature.com/news](http://www.nature.com/news)

**From:** [Stevens, Timothy](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Newman, Jamie <newman@rti.org> \(newman@rti.org\)](#)  
**Subject:** FW: Breathing Outcomes  
**Date:** Thursday, October 17, 2013 10:43:46 AM  
**Attachments:** [Breathing Outcomes Update - October 2013.pptx](#)

---

Hi Rose and Jamie

Please see below.

Thanks

Tim

---

**From:** Stevens, Timothy  
**Sent:** Wednesday, October 16, 2013 10:01 PM  
**To:** Newman, Jamie <newman@rti.org> (newman@rti.org)  
**Subject:** Breathing Outcomes

Hi Jamie

Can these slides be shown tomorrow as part of my update?

Am I still on for 3:25?

Thanks

Tim

# Breathing Outcomes Update

October 2013

# Breathing Outcomes Manuscript

## *Main Findings*

- One or more interviews were completed for 918 of 922 (99.6%) eligible infants.
- The incidence of wheezing and cough were 47.9% and 31.0%, respectively, and did not differ between study arms of either randomized intervention.
- Among secondary outcomes, infants randomized to low versus high oxygen saturation targets had a lower incidence of wheezing (36.3% vs. 43.4%,  $p < 0.05$ ).
- Infants randomized to CPAP versus intubation/surfactant had
  - fewer episodes of wheezing without a cold (28.9% vs. 36.5%,  $p < 0.05$ )
  - respiratory illnesses diagnosed by a doctor (47.7% vs. 55.2%,  $p < 0.05$ )
  - physician or emergency room visits for breathing problems (68.0% vs. 72.9%,  $p < 0.05$ ) through 18-22 months CA.

# Manuscript Submission - Pediatrics

- Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT)
  - March 2013 - Submitted to Pediatrics
  - May 2013 - invited to resubmit with changes
  - July 2013 - resubmitted to Pediatrics
  - August 2013 – rejected by Pediatrics. “It is a nice description of .... pragmatic respiratory outcomes, but of limited interest to the medical community.”

# Manuscript Submission – J Peds

- August 2013 – Submit to J. Peds
- October 2013 – invited to resubmit
  - Selected comments
    - “Also, as the initial study was a 2X2 factorial design, did any of the group combinations lead to worse or better measured outcomes? “
    - “Did the CPAP patients that never required intubation and mechanical ventilation do better? Details such as these would assist in interpreting the data from this follow-up cohort.”
  - In revision

# Second Manuscript

Draft PAS Abstract to be circulated for review by 10/24

- Predictors of Respiratory Outcomes from the SUPPORT Trial
  - BPD and respiratory outcomes
  
  - Multivariate analysis of family history, inpatient outcomes (e.g. BPD, treatment assignment) and outpatient exposures (e.g. tobacco, RSV, daycare) predicting
    - Symptoms (wheezing and cough)
    - Illnesses (bronchiolitis, pneumonia, bronchitis)
    - Health service use (physician or ED, hospital visits)

# Traditional BPD and Respiratory Outcomes

	Traditional BPD N=378	Not Traditional BPD N=524	ARR (95% CI)	P-Value
<b>Primary Outcomes</b>				
Has your child's chest sounded wheezy or whistling more than twice in one week?	194 (51.7)	242 (44.7)	1.53 (1.15, 2.02)	<0.01
Has your child had a cough for more than 3 days without a cold?	103 (36.9)	130 (30.4)	1.29 (0.91, 1.82)	0.15
<b>Secondary Outcomes</b>				
<b>Symptoms</b>				
Wheezing/whistling more than twice in one week or cough more than 3 days	210 (75.3)	279 (65.3)	1.83 (1.25, 2.68)	<0.01
Has your child's chest sounded wheezy or whistling?	181 (64.9)	254 (59.3)	1.67 (1.12, 2.49)	0.01
Has your baby's chest sounded wheezy or whistling apart from colds?	104 (37.3)	132 (30.9)	1.49 (1.06, 2.10)	0.02

*Adjusted for GA, Familial Clustering, and Center*

# Traditional BPD and Respiratory Outcomes

<b><u>Outcomes</u></b>	<b>Traditional</b>	<b>Not</b>	<b><u>ARR (95% CI)</u></b>	<b><u>P-Value</u></b>
	<b>BPD</b>	<b>Traditional</b>		
	<b><u>N=378</u></b>	<b><u>N=524</u></b>		
<b><u>Illnesses</u></b>				
<b>Has your child had asthma, reactive airway disease or BPD flare-up diagnosed by a doctor?</b>	108 (38.8)	139 (32.5)	1.31 (1.05, 1.65)	0.02
<b>Has your child had bronchiolitis, bronchitis or pneumonia diagnosed by a doctor?</b>	120 (42.7)	163 (38.3)	1.37 (0.99, 1.89)	0.06
<b>Has your child had croup diagnosed by a doctor?</b>	29 (10.4)	52 (12.2)	0.71 (0.46, 1.10)	0.13
<b><u>Health Services</u></b>				
<b>Has your child ever had to visit the doctor for breathing or wheezing problems?</b>	191 (69.0)	264 (62.1)	0.74 (0.52, 1.04)	0.08
<b>Has your child had to stay in a hospital overnight?</b>	145 (51.8)	160 (37.4)	0.46 (0.33, 0.65)	<0.01
<b>Has your child had to stay in a hospital overnight for wheezing/breathing problems?</b>	107 (38.2)	118 (27.6)	0.54 (0.39, 0.76)	<0.01

*Adjusted for GA, Familial Clustering, and Center*

# Traditional BPD and Respiratory Outcomes

<u>Outcomes</u>	Not		<u>ARR (95% CI)</u>	<u>P-Value</u>
	<u>Traditional</u>	<u>Traditional</u>		
	<u>BPD</u>	<u>BPD</u>		
	<u>N=378</u>	<u>N=524</u>		
<u>Medications</u>				
Treated with a diuretic medication?	47 (12.5)	8 (1.5)	15.35 (7.11, 33.12)	<0.01
Treated with an inhaled steroid medication?	135 (35.9)	106 (19.6)	2.43 (1.77, 3.32)	<0.01
Treated with a nebulized medication?	35 (9.3)	36 (6.7)	1.45 (0.88, 2.39)	0.14
Treated with a systemic steroid medication?	40 (10.7)	46 (8.5)	1.49 (0.95, 2.33)	0.08
Treated with oxygen at home?	132 (46.8)	27 (6.4)	11.80 (6.96, 19.99)	<0.01
<u>Family</u>				
Have you had to change your plans because of your child's breathing problems?	111 (39.8)	143 (33.4)	0.76 (0.55, 1.05)	0.1

*Adjusted for GA, Familial Clustering, and Center*

**From:** Luc Brion  
**To:** Roy Heyne; Wally Carlo; Wrage, Lisa Ann; Myra Wyckoff; Mambarambath Jaleel; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [E]; "Gantz, Marie"; Das, Abhik; Barbara Stoll; Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu  
**Subject:** RE: Updated information re LeVan's paper about change in practice after SUPPORT  
**Date:** Wednesday, October 16, 2013 4:39:08 PM

---

Roy

Oops sent it before completing the sentence

Thanks for your response.

You are correct; in the proposed response to reviewers, any information on the survey is based on UTSW (Parkland) data only. This will be updated when we have all the results of the survey

Luc

**From:** Roy Heyne  
**Sent:** Wednesday, October 16, 2013 2:50 PM  
**To:** Luc Brion; Wally Carlo; Wrage, Lisa Ann; Myra Wyckoff; Mambarambath Jaleel; (b)(6)@gmail.com; Rosemary Higgins; 'Gantz, Marie'; Das, Abhik; Barbara Stoll; Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu  
**Subject:** RE: Updated information re LeVan's paper about change in practice after SUPPORT

Luc, the slides still look fine and the proposed responses look reasonable. I assume the ones citing survey responses are still preliminary.

**From:** Luc Brion  
**Sent:** Tuesday, October 15, 2013 10:28 PM  
**To:** Wally Carlo; Wrage, Lisa Ann; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; (b)(6)@gmail.com; Rosemary Higgins; 'Gantz, Marie'; Das, Abhik; Barbara Stoll; Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu; Luc Brion; Roy Heyne  
**Subject:** Updated information re LeVan's paper about change in practice after SUPPORT

I have updated

1. The tentative Powerpoint presentation for Thursday; I will only present the first 9 slides; the other slides are backup for potential questions
2. The proposed response to reviewers; I made several changes

Please let me know if you have any comments or suggestions

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.

**From:** Luc Brion  
**To:** Wally Carlo; Wraga, Lisa Ann; Roy Heyne; Myra Wyckoff; Mambarambath Jaleel; (b)(6)@gmail.com; Higgins, Rosemary (NIH/NICHD) [F]; "Gantz, Marie"; Das, Abhik; Barbara Stoll; Pablo.Sanchez@nationwidechildrens.org; nfiner@ucsd.edu; Luc Brion; Roy Heyne  
**Subject:** Updated information re LeVan's paper about change in practice after SUPPORT  
**Date:** Tuesday, October 15, 2013 11:28:37 PM  
**Attachments:** [Change in Practice rev2.pptx](#)  
[Responses to reviewers 101513.docx](#)

---

I have updated

1. The tentative Powerpoint presentation for Thursday; I will only present the first 9 slides; the other slides are backup for potential questions
2. The proposed response to reviewers; I made several changes

Please let me know if you have any comments or suggestions

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

Ref.: Ms. No. 20131573

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members is a separate Appendix file. The figure is at 1000 dpi. We labeled the third table as online only. We include an itemized list of responses to the reviewers.

We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.

*Response: The text of the first version had 2697 words; the revised version has 2410 words. The text of the discussion was shortened by ½ page. We have shortened the results section by removing all numbers from the text that were in Figure 1 or in the tables.*

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.jpeds.com/authorinfo>).

*Response: We have shortened the abstract; it contains 197 words. The abstract is structured as indicated.*

Please upload the list of Study Group members as a separate Appendix file.

*Response: the list of Study Group is a separate file.*

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

*Response: Figures are submitted at TIFF files with 1,000 dpi.*

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the

file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

*Response: we have changed online documents as requested.*

Itemized responses to Reviewers:

Reviewer #1: (b)(4),(b)(5),(b)(6)

(b)(4),(b)(5),(b)(6)

Page 0774 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0775 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0776 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0777 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0778 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0779 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0780 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 0781 of 2000

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(b)(4)

of the Freedom of Information and Privacy Act

Page 0782 of 2000

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(b)(4)

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(b)(4)

of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

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Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

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(b)(4)

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Page 0790 of 2000

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Page 0791 of 2000

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Page 0792 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 0793 of 2000

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

**From:** Luc Brion  
**To:** Myra Wyckoff; Roy Heyne; (b)(6)@gmail.com; "nfiner@ucsd.edu"; "Wally Carlo"; "Abhik Das"; "Gantz, Marie"; "Barbara Stoll"; "Wraga, Lisa Ann"; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Please review; response to reviewers to Jackie LeVan's study on changes after SUPPORT; presentation planned on Thursday at NRN  
**Date:** Tuesday, October 15, 2013 1:33:24 AM  
**Attachments:** Survey re Jackie LeVan's paper SUPPORT 10-11-13 rev.docx  
Change in Practice.pptx  
Responses to reviewers 101013.docx

---

Dear Colleagues:

As discussed, J Peds reviewers asked for several additional analyses for Jackie's study on change in practice after SUPPORT.

I need committee approval before new analyses could be done.

Barbara gave me the green light, and Abhik has allowed me to present this at the steering committee.

Could you please review this first draft of my presentation on Thursday.

Final decision will need Rose Higgins' vote after the meeting.

Attached:

1. Proposed survey
2. Proposed itemized response to reviewers; Lisa will be running the other analyses listed in the Word document.
3. Proposed presentation to steering committee

Thanks

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal  
Medicine  
The University of Texas Southwestern Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-  
9063  
Office: (214) 648-3903  
Fax: (214) 648-2481  
luc.brion@utsouthwestern.edu

+++++CONFIDENTIALITY NOTICE+++++

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### Changes in Therapy and Outcomes in 24-27<sup>0/7</sup> week GA infants Associated with The SUPPORT Trial

Survey - Table of Confounding Variables, 10/11/13

	1/1/2003-12/31/2004			1/1/2010-12/31/2012			Time of change; primarily/directly in response to the publication of SUPPORT results
Practice	Details of Intervention	Indications/Contraindications	Written Policy (P)/ Guideline (G)	Details of Intervention	Indication	Written Policy (P)/ Guideline (G)	
Prenatal Steroids	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications: _____  - Contraindications: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications: _____  - Contraindications: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Intrapartum Magnesium for neuroprotection	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Magnesium use for preeclampsia	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
DR cardiac massage or medications	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
T piece resuscitators in DR	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of CPAP in DR	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of PEEP in DR	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Starting FiO2 in DR	-100 %O2 <input type="checkbox"/> -40% O2 <input type="checkbox"/> -21% O2 <input type="checkbox"/> -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/Respiratory distress/resusc <input type="checkbox"/> -O2 for sat < goal <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-100 %O2 <input type="checkbox"/> -40% O2 <input type="checkbox"/> -21% O2 <input type="checkbox"/> -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress/resusc <input type="checkbox"/> -O2 for sat < goal <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of preductal pulse oximeter in	-	- All <input type="checkbox"/> -None <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____

DR to adjust FiO2		- Any resuscitation <input type="checkbox"/> - Other _____			- Any resuscitation <input type="checkbox"/> - Other _____		Primarily response to SUPPORT publication <input type="checkbox"/>
Saturation goals in DR	-High (similar to NICU) <input type="checkbox"/> -Low (based on postnatal age increase) <input type="checkbox"/>	- All <input type="checkbox"/> -None <input type="checkbox"/> -Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-High (similar to NICU) <input type="checkbox"/> -Low(NRP: based on postnatal age increase) <input type="checkbox"/>	- All <input type="checkbox"/> -None <input type="checkbox"/> -Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Temperature control in DR	-Warmer <input type="checkbox"/> -Gel pad <input type="checkbox"/> -Plastic bag <input type="checkbox"/> -Hat <input type="checkbox"/> -Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Warmer <input type="checkbox"/> -Gel pad <input type="checkbox"/> -Plastic bag <input type="checkbox"/> -Hat <input type="checkbox"/> -Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Participation in COIN/Feasibility Trial	- COIN <input type="checkbox"/> - Feasibility <input type="checkbox"/>	-	-	-	-	-	-
Golden hour upon NICU admission	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation target range in NICU	_____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	_____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation lower and upper limits in NICU	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Adjustment of oxygen administration for procedures	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Surfactant administration	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Vitamin A prophylaxis	-	- All <input type="checkbox"/> -None <input type="checkbox"/> -<1 kg <input type="checkbox"/> - < ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Available <input type="checkbox"/> - Not available x	- All <input type="checkbox"/> -None <input type="checkbox"/> -<1 kg <input type="checkbox"/> - < ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>

Caffeine/theophylline	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Prophylactic indomethacin or ibuprofen	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - None <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - None <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Physiologic testing for BPD	-	- Per NIH protocol <input type="checkbox"/> - None <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- Per NIH protocol <input type="checkbox"/> - None <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for CLD/BPD	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for hypotension	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
PDA medical closure	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
PDA surgical closure	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>

# SUPPORT RESULTS

- CPAP trial:
  - Death or BPD: not significantly different (CPAP vs. surfactant)
  - In the CPAP group:
    - Lower proportion: endotracheal intubation, postnatal steroids for BPD
    - Fewer days of mechanical ventilation among survivors,
    - More likely to be alive and off mechanical ventilation by day seven.
    - Among infants with GA 24<sup>0/7</sup> - 25<sup>6/7</sup> weeks, lower risk of death during hospitalization and at 36 weeks postmenstrual age (PMA)
    - Less use of epinephrine in the DR
- Saturation target trial:
  - Severe ROP or death: not significantly different between the two oxygen saturation target groups.
  - Risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

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of the Freedom of Information and Privacy Act

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

Ref.: Ms. No. 20131573

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Wright and Balistreri:

Thank you for your email dated 10/4/13. We have revised the manuscript as you requested. We have focused the discussion. We have removed all redundancy between sections of text, between tables and text, and between illustrations and text. The Abstract is <250 words. The list of Study Group members is a separate Appendix file. The figure is at 1000 dpi. We labeled the third table as online only. We include an itemized list of responses to the reviewers.

We thank you for your consideration and hope this revised manuscript meets expectation for publication.

Luc P Brion, MD

Itemized responses to the Editors:

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text.

*Response: The text of the first version had 2697 words; the revised version has 2410 words. The text of the discussion was shortened by ½ page. We have shortened the results section by removing all numbers from the text that were in Figure 1 or in the tables.*

Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.jpeds.com/authorinfo>).

*Response: We have shortened the abstract; it contains 197 words. The abstract is structured as indicated.*

Please upload the list of Study Group members as a separate Appendix file.

*Response: the list of Study Group is a separate file.*

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

*Response: Figures are submitted at TIFF files with 1,000 dpi.*

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the

file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

*Response: we have changed online documents as requested.*

**Itemized responses to Reviewers:**

**Reviewer #1:** (b)(4),(b)(5),(b)(6)

(b)(4),(b)(5),(b)(6)

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(b)(4),(b)(5),(b)(6)

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(b)(4),(b)(5),(b)(6)

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(b)(4),(b)(5),(b)(6)

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Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

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**From:** Luc Brion  
**To:** (b)(6)@gmail.com; Myra Wyckoff; Mambarambath, Jaleel; Roy Heyne; "Barbara Stoll"; "Wally Carlo"; "Wright, Lisa Ann"; "Abhik Das"; "Gantz, Marie"; Pablo.Sanchez@nationwidechildrens.org; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"  
**Subject:** Updated survey of practices re Jacky LeVan's paper on change in practice after SUPPORT  
**Date:** Friday, October 11, 2013 11:06:46 PM  
**Attachments:** Survey re Jackie LeVan's paper SUPPORT 10-11-13 rev.docx  
Survey re Jackie LeVan's paper SUPPORT 10-11-13 PHHS rev.docx

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After discussing with Barbara Stoll, Roy Heyne, Myra Wyckoff and Mambarambath Jaleel, here are more edits on the proposed survey.

I also attach the completed form for Parkland (work in progress).

The survey asks questions about SUPPORT-related procedures and other procedures, in response to the reviewers' questions about why death/BPD, death/ROP and other outcomes improved after SUPPORT but not with randomization during SUPPORT, suggesting that changes in outcomes might be related to changes in other practices, rather than changes related to SUPPORT results.

Please review and let me know.

Best regards,

Luc

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Director, Fellowship Training Program in Neonatal-Perinatal  
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### Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial

Survey - Table of Confounding Variables, 10/11/13

	1/1/2003-12/31/2004			1/1/2010-12/31/2012			Time of change; primarily/directly in response to the publication of SUPPORT results
Practice	Details of Intervention	Indications/Contraindications	Written Policy (P)/ Guideline (G)	Details of Intervention	Indication	Written Policy (P)/ Guideline (G)	
Prenatal Steroids	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications: _____  - Contraindications: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications: _____  - Contraindications: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Intrapartum Magnesium for neuroprotection	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Magnesium use for preeclampsia	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
DR cardiac massage or medications	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
T piece resuscitators in DR	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of CPAP in DR	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of PEEP in DR	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Anesthesia bag <input type="checkbox"/> -T piece <input type="checkbox"/> - Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Starting FiO2 in DR	-100 %O2 <input type="checkbox"/> -40% O2 <input type="checkbox"/> -21% O2 <input type="checkbox"/> -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/Respiratory distress/resusc <input type="checkbox"/> -O2 for sat < goal <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-100 %O2 <input type="checkbox"/> -40% O2 <input type="checkbox"/> -21% O2 <input type="checkbox"/> -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress/resusc <input type="checkbox"/> -O2 for sat < goal <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Use of preductal pulse oximeter in	-	- All <input type="checkbox"/> -None <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____

DR to adjust FiO2		- Any resuscitation <input type="checkbox"/> - Other _____			- Any resuscitation <input type="checkbox"/> - Other _____		Primarily response to SUPPORT publication <input type="checkbox"/>
Saturation goals in DR	-High (similar to NICU) <input type="checkbox"/> -Low (based on postnatal age increase) <input type="checkbox"/>	- All <input type="checkbox"/> -None <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-High (similar to NICU) <input type="checkbox"/> -Low(NRP; based on postnatal age increase) <input type="checkbox"/>	- All <input type="checkbox"/> -None <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Temperature control in DR	-Warmer <input type="checkbox"/> -Gel pad <input type="checkbox"/> -Plastic bag <input type="checkbox"/> -Hat <input type="checkbox"/> -Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Warmer <input type="checkbox"/> -Gel pad <input type="checkbox"/> -Plastic bag <input type="checkbox"/> -Hat <input type="checkbox"/> -Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Participation in COIN/Feasibility Trial	- COIN <input type="checkbox"/> - Feasibility <input type="checkbox"/>	-	-	-	-	-	-
Golden hour upon NICU admission	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> -None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation target range in NICU	_____	- All <input type="checkbox"/> - Varies with postnatal age  - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	_____	- All <input type="checkbox"/> - Varies with postnatal age  - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation lower and upper limits in NICU	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age  - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age  - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Adjustment of oxygen administration for procedures	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Surfactant administration	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>
Vitamin A prophylaxis	-	- All <input type="checkbox"/> -None <input type="checkbox"/> -<1 kg <input type="checkbox"/> -< ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Available <input type="checkbox"/> - Not available x	- All <input type="checkbox"/> -None <input type="checkbox"/> -<1 kg <input type="checkbox"/> -< ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____ Primarily response to SUPPORT publication <input type="checkbox"/>

Caffeine/theophylline	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Prophylactic indomethacin or ibuprofen	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - None <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - None <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Physiologic testing for BPD	-	- Per NIH protocol <input type="checkbox"/> - None <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- Per NIH protocol <input type="checkbox"/> - None <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for CLD/BPD	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for hypotension	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
PDA medical closure	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>
PDA surgical closure	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	Time of change: _____  Primarily response to SUPPORT publication <input type="checkbox"/>

**Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial**

Survey - Table of Confounding Variables, 10/11/13 – Parkland data

	1/1/2003-12/31/2004			1/1/2010-12/31/2012			Changes primarily/directly in response to the publication of SUPPORT results
Practice	Details of Intervention	Indications Contraindications	Written Policy (P)/ Guideline (G)	Details of Intervention	Indication	Written Policy (P)/ Guideline (G)	
Prenatal Steroids	- Dexamethasone x - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective x - Indications:  - Contraindications: Preeclampsia, Diabetes mellitus	- P x - G <input type="checkbox"/>	- Dexamethasone <input type="checkbox"/> - Betamethasone x	- All <input type="checkbox"/> - Selective x - Indications:  - Contraindications: Preeclampsia, Diabetes mellitus	- P x - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
Intrapartum Magnesium for neuroprotection	-	- All <input type="checkbox"/> - None x - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> - None <input type="checkbox"/> - < 28 weeks x - Other: _____	- P x - G <input type="checkbox"/>	4/2010 Primarily response to SUPPORT publication <input type="checkbox"/>
Magnesium use for preeclampsia	-	- All x - Other: _____	- P x - G <input type="checkbox"/>	-	- All x - Other: _____	- P x - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
DR cardiac massage or medications	- Per NRP x - Other: _____	- If effective ventilation fails to improve HR x - Other _____	- P x - G <input type="checkbox"/>	- Per NRP x - Other: _____	- If effective ventilation fails to improve HR x - Other _____	- P x - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
T piece resuscitators in DR	-	- All <input type="checkbox"/> - None x - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All <input type="checkbox"/> - None <input type="checkbox"/> - Apnea/respiratory distress x	- P <input type="checkbox"/> - G x	2005 before SUPPORT Primarily response to SUPPORT publication <input type="checkbox"/>
Use of CPAP in DR	-Anesthesia bag x -T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress x	- P <input type="checkbox"/> - G x	-Anesthesia bag x -T piece x - Bubble CPAP <input type="checkbox"/> -Ventilator <input type="checkbox"/>	- All x - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G x	May 1, 2011 Primarily response to SUPPORT publication X
Use of PEEP in DR	-Anesthesia bag x -T piece <input type="checkbox"/> -Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress x	- P <input type="checkbox"/> - G x	-Anesthesia bag x -T piece x -Ventilator <input type="checkbox"/> - PEEP valve <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress x	- P <input type="checkbox"/> - G x	Primarily response to SUPPORT publication <input type="checkbox"/>
Starting FiO2 in DR	-100 %O2 x -40% O2 <input type="checkbox"/> -21% O2 <input type="checkbox"/> -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress/resusc x -O2 for sat < goal <input type="checkbox"/>	- P <input type="checkbox"/> - G x	-100 %O2 <input type="checkbox"/> -40% O2 <input type="checkbox"/> -21% O2 x -Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress/resusc <input type="checkbox"/> O2 for sat < goal x	- P <input type="checkbox"/> - G x	4/2011 Primarily response to SUPPORT publication <input type="checkbox"/>
Use of preductal pulse oximeter in DR to adjust FiO2	-	- All <input type="checkbox"/> - None <input type="checkbox"/> - Any resuscitation <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All x - None <input type="checkbox"/>	- P <input type="checkbox"/> - G x	4/2011 Primarily response to SUPPORT publication <input type="checkbox"/>

		- Other _____			- Any resuscitation <input type="checkbox"/> - Other _____		
Saturation goals in DR	-High (similar to NICU) <input type="checkbox"/> -Low (based on postnatal age increase) <input type="checkbox"/> -None x	- All <input type="checkbox"/> - None x - Any resuscitation <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-High (similar to NICU) <input type="checkbox"/> -Low(NRP; based on postnatal age increase) x	- All x - None <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G x	4/2011 Primarily response to SUPPORT publication <input type="checkbox"/>
Temperature control in DR	-Warmer x -Gel pad x -Plastic bag x -Hat x -Blankets x	- All x - GA-specific: _____	- P x - G <input type="checkbox"/>	-Warmer x -Gel pad x -Plastic bag x -Hat x -Blankets x	- All x - GA-specific: _____	- P x - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
Participation in COIN/Feasibility Trial	- COIN <input type="checkbox"/> - Feasibility <input type="checkbox"/>	-	-	NA	-	-	Primarily response to SUPPORT publication <input type="checkbox"/>
Golden hour upon NICU admission	- <input type="checkbox"/>	- All <input type="checkbox"/> - None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- All x - None <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G x	4/2012 Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation target range in NICU	88-94%	- All x - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P x - G <input type="checkbox"/>	88-94%	- All x - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P x - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal O2 saturation lower and upper limits in NICU	Low: <u>80</u> _____ High: <u>95</u> _____	- All x - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P x - G <input type="checkbox"/>	Low: <u>85</u> _____ High: <u>95</u> _____	- All x - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P x - G <input type="checkbox"/>	Early 2012 Primarily response to SUPPORT publication <input type="checkbox"/>
Adjustment of oxygen administration for procedures	-Preoxygenation x -Adjust FiO2 based on saturation <input type="checkbox"/>	- All x - None <input type="checkbox"/> - Other _____	- P x - G <input type="checkbox"/>	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation x	- All x - None <input type="checkbox"/> - Other _____	- P x - G <input type="checkbox"/>	Early 2012 Primarily response to SUPPORT publication <input type="checkbox"/>
Surfactant administration	-DR <input type="checkbox"/> -NICU x -Bagging x -On ventilator <input type="checkbox"/> -100% O2 x -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS x	- P <input type="checkbox"/> - G x	-DR <input type="checkbox"/> -NICU x -Bagging x -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed x	-Prophylaxis <input type="checkbox"/> -Only if RDS x	- P x - G <input type="checkbox"/>	G (O2): Early 2012 P: 4/2013 Primarily response to SUPPORT publication <input type="checkbox"/>
Vitamin A prophylaxis	-	- All <input type="checkbox"/> - None <input type="checkbox"/> -<1 kg x -< ___ weeks	- P <input type="checkbox"/> - G x	Available <input type="checkbox"/> Not available x	- All <input type="checkbox"/> - None <input type="checkbox"/> -<1 kg x -< ___ weeks	- P <input type="checkbox"/> - G x	Not available in 2 <sup>nd</sup> cohort Primarily response to SUPPORT publication <input type="checkbox"/>
Caffeine/theophylline	-Caffeine <input type="checkbox"/> -Theophylline x	-If apnea x -Prophylaxis <1250g <input type="checkbox"/>	- P <input type="checkbox"/> - G x	-Caffeine x -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g x	- P x - G x	G 1/2010; P 7/2012 Primarily response to

		-Other: _____			-Other: _____		SUPPORT publication <input type="checkbox"/>
Prophylactic indomethacin or ibuprofen	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> -None <input type="checkbox"/> -Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> -None -Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Primarily response to SUPPORT publication <input type="checkbox"/>
Physiologic testing for BPD	-	- Per NIH protocol <input type="checkbox"/> - No <input type="checkbox"/> Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-	- Per NIH protocol x - No <input type="checkbox"/> -Other <input type="checkbox"/>	- P x - G <input type="checkbox"/>	02/2008 Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for CLD/BPD	-Dexamethasone x -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD x -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G x	-Dexamethasone x -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD x -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G x	Primarily response to SUPPORT publication <input type="checkbox"/>
Postnatal Steroids for hypotension	-Hydrocortisone x -Other _____	-Severe x - Other _____	- P <input type="checkbox"/> - G x	-Hydrocortisone x -Other _____	-Severe x - Other _____	- P <input type="checkbox"/> - G x	Primarily response to SUPPORT publication <input type="checkbox"/>
PDA medical closure	-Indomethacin x -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week x - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G x	-Indomethacin x -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1week x - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G x	Primarily response to SUPPORT publication <input type="checkbox"/>
PDA surgical closure	-Bedside Surgery x -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated x - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G x	-Bedside Surgery x -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated x - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G x	Primarily response to SUPPORT publication <input type="checkbox"/>

**From:** Luc Brion  
**To:** (b)(6)@gmail.com; Myra Wyckoff; Mambarambath Jaleel; Roy Heyne; Barbara Stoll; Wally Carlo; Wraga, Lisa Ann; Abhik Das; "Gantz, Marie"; Pablo.Sanchez@nationwidechildrens.org; Higgins, Rosemary (NIH/NICHD) [E]; "nfiner@ucsd.edu"  
**Subject:** Proposed survey of centers for the manuscript on practice change after SUPPORT  
**Date:** Friday, October 11, 2013 12:10:33 PM  
**Attachments:** Survey re Jackie LeVan's paper SUPPORT 10-11-13.docx  
Survey re Jackie LeVan's paper SUPPORT Parkland 10-11-13.docx

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I attach the completed survey of center practices for Parkland (with minor edits) as an example. I also attach an alternative template, with checkboxes to ease data entry as suggested by Barbara. Please review and let me know.

Best regards,  
Luc

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**Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial**  
 Survey - Table of Confounding Variables, 10/11/13

	1/3-1/5			7/12-6/14		
	Details of Intervention	Indications/ Contraindications	Written Policy (P)/ Guideline (G)	Details of Intervention	Indication	Policy (P)/ Guideline (G)
Prenatal Steroids	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications:  - Contraindications:  	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Dexamethasone <input type="checkbox"/> - Betamethasone <input type="checkbox"/>	- All <input type="checkbox"/> - Selective <input type="checkbox"/> - Indications:  - Contraindications:  	- P <input type="checkbox"/> - G <input type="checkbox"/>
Intrapartum Magnesium for neuroprotection	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - < 28 weeks <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Magnesium use for preeclampsia	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
DR cardiac massage or medications	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Per NRP <input type="checkbox"/> - Other: _____	- If effective ventilation fails to improve HR <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
T piece resuscitators in DR	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Use of CPAP in DR	- Anesthesia bag <input type="checkbox"/> - T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Anesthesia bag <input type="checkbox"/> - T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/>	- All <input type="checkbox"/> - Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Use of PEEP in DR	- Anesthesia bag <input type="checkbox"/> - T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Anesthesia bag <input type="checkbox"/> - T piece <input type="checkbox"/> - Bubble CPAP <input type="checkbox"/>	- All <input type="checkbox"/> - Apnea/Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Starting FiO2 in DR	- 100% O2 <input type="checkbox"/> - 40% O2 <input type="checkbox"/> - 21% O2 <input type="checkbox"/> - Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- 100% O2 <input type="checkbox"/> - 40% O2 <input type="checkbox"/> - 21% O2 <input type="checkbox"/> - Other _____	- O2 for All <input type="checkbox"/> - O2 for apnea/ Respiratory distress <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Use of productal pulse oximeter in DR to adjust FiO2	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Saturation goals in DR	- High <input type="checkbox"/> - Low <input type="checkbox"/> - None <input type="checkbox"/>	- All <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- High <input type="checkbox"/> - Low <input type="checkbox"/> - None <input type="checkbox"/>	- All <input type="checkbox"/> - Any resuscitation <input type="checkbox"/> - Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Temperature control in DR	- Warmer <input type="checkbox"/> - Gel pad <input type="checkbox"/> - Plastic bag <input type="checkbox"/> - Hat <input type="checkbox"/> - Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific:  	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Warmer <input type="checkbox"/> - Gel pad <input type="checkbox"/> - Plastic bag <input type="checkbox"/> - Hat <input type="checkbox"/> - Blankets <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific:  	- P <input type="checkbox"/> - G <input type="checkbox"/>

Participation in COIN/Feasibility Trial	- COIN <input type="checkbox"/> - Feasibility <input type="checkbox"/>	-	-	- COIN <input type="checkbox"/> - Feasibility <input type="checkbox"/>	-	-
Golden hour upon NICU admission	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> - GA-specific: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Postnatal O2 saturation target range in NICU	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Postnatal O2 saturation lower and upper limits in NICU	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	Low: _____ High: _____	- All <input type="checkbox"/> - Varies with postnatal age _____ - Varies with Postmenstrual age _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Adjustment of oxygen administration for procedures	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Preoxygenation <input type="checkbox"/> -Adjust FiO2 based on saturation <input type="checkbox"/>	- All <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Surfactant administration	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-DR <input type="checkbox"/> -NICU <input type="checkbox"/> -Bagging <input type="checkbox"/> -On ventilator <input type="checkbox"/> -100% O2 <input type="checkbox"/> -O2 as needed <input type="checkbox"/>	-Prophylaxis <input type="checkbox"/> -Only if RDS <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Vitamin A prophylaxis	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> -<1 kg <input type="checkbox"/> - < ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- All <input type="checkbox"/> -<1 kg <input type="checkbox"/> - < ___ weeks	- P <input type="checkbox"/> - G <input type="checkbox"/>
Caffeine/theophylline	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Caffeine <input type="checkbox"/> -Theophylline <input type="checkbox"/>	-If apnea <input type="checkbox"/> -Prophylaxis <1250g <input type="checkbox"/> -Other: _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Prophylactic indomethacin or ibuprofen	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/> -No <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/> -No <input type="checkbox"/>	-<1250 g <input type="checkbox"/> -<1000 g <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
Physiologic testing for BPD	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- Per NIH protocol <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	- Yes <input type="checkbox"/> - No <input type="checkbox"/>	- Per NIH protocol <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Postnatal Steroids for CLD/BPD	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Dexamethasone <input type="checkbox"/> -Betamethasone <input type="checkbox"/> -Hydrocortisone <input type="checkbox"/>	-Severe CLD/BPD <input type="checkbox"/> -Other <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>
Postnatal Steroids for hypotension	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Hydrocortisone <input type="checkbox"/> -Other _____	-Severe <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>

PDA medical closure	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1 week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Indomethacin <input type="checkbox"/> -Ibuprofen <input type="checkbox"/>	-Symptomatic, moderate/severe PDA, intubated > 1 week <input type="checkbox"/> - Symptomatic, moderate/severe PDA, any age <input type="checkbox"/> - Moderate/severe on echo <input type="checkbox"/> - Other _____	- P <input type="checkbox"/> - G <input type="checkbox"/>
PDA surgical closure	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>	-Bedside Surgery <input type="checkbox"/> -OR <input type="checkbox"/>	- After Medical therapy without response or contraindicated <input type="checkbox"/> - First approach <input type="checkbox"/>	- P <input type="checkbox"/> - G <input type="checkbox"/>

**Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial**  
**Survey - Table of Confounding Variables, 10/11/13**

	1/3-1/5			7/12-6/14		
	Details of Intervention	Indication	Policy (P)/ Guideline (G)	Details of Intervention	Indication	Policy (P)/ Guideline (G)
Prenatal Steroids	Dexamethasone	All but preeclampsia or IDM	P	Betamethasone	All but preeclampsia or IDM	P
Intrapartum Magnesium use for neuroprotection	No	-	-	Yes	All <28 weeks started 4/2010	P
Magnesium use for preeclampsia	Yes	All	P	Yes	All	P
DR cardiac massage or medications	Per NRP	If effective ventilation does not improve HR	P	Per NRP	If effective ventilation does not improve HR	P
T piece resuscitators in DR	No	-	-	Yes	Respiratory distress	G
Use of CPAP in DR	Anesthesia bag	Respiratory distress	G	Anesthesia bag/ T piece	Respiratory distress	G
Use of PEEP in DR	Anesthesia bag	Apnea or respiratory distress	G	Anesthesia bag/ T piece	Apnea or respiratory distress	G
Starting FiO2 in DR	100% O2	Apnea or respiratory distress	G	21%	All	G (4/2011)
Use of preductal pulse oximeter in DR to adjust FiO2	No	-	-	Yes	All	G
Saturation goals in DR	-	-	-	Low sat goals Per NRP	All	G (4/2011)
Temperature control in DR	Gel pad, blankets, hat, plastic bag	All	P	Gel pad, blankets, hat, plastic bag	All	P
Participation in COIN/Feasibility trial	COIN: No Feasibility Trial: No	-	-	-	-	-
Golden hour upon NICU admission	-	-	-	Yes	All	G
Postnatal O2 saturation target range in NICU	88-94%	All	P	88-94%	All	P (Early 2012)
Postnatal O2 saturation lower and upper limits in NICU	80-95%	All	P	85-95%	All	P
Adjustment of oxygen administration for procedures	Preoxygenation before procedures (suctioning) using 100% O2	All	P	No preoxygenation; Adjustment of FiO2 to pulse oximetry	All	P

Surfactant administration	In NICU with 100%O2 and bag and mask	If RDS demonstrated based on chest X ray and O2 requirement	G	In NICU with bag and mask and FiO2 titrated based on pulse oximetry	If RDS demonstrated based on chest X ray and O2 requirement	G
Vitamin A prophylaxis	Yes	<1 kg	G	-	Not available	G
Caffeine	Theophylline	If Apnea	G	Caffeine	Prophylaxis <1250 grams (CAP trial)	G
Prophylactic indomethacin or ibuprofen	No	-	G	No	-	G
Physiologic testing for BPD	No	-	-	Yes	All	P
Postnatal Steroids	Dex (BPD)/hydrocortisone (hypotension)	Severe CLD or BPD/severe hypotension	G	Dex (BPD)/hydrocortisone (hypotension)	Severe CLD or BPD/severe hypotension	G
PDA medical closure	Indomethacin	Symptomatic moderate/large PDA, intubated at > 1 week	G	Indomethacin	Symptomatic moderate/large PDA, intubated at > 1 week	G
PDA surgical closure	Bedside surgery	Symptomatic moderate/large PDA, intubate at > 1 week, no response or contraindication to indomethacin	G	Bedside surgery	Symptomatic moderate/large PDA, intubate at > 1 week, no response or contraindication to indomethacin	G

**From:** Luc Brion  
**To:** (b)(6)@gmail.com; Wraga, Lisa Ann; "Gantz, Marie"; Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org; Roy Heyne; Mambarambath Jaleel; "nfiner@ucsd.edu"; Wally Carlo; Abhik Das; Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion  
**Subject:** FW: Your Manuscript # 20131573 submitted to JPediatr - ASKING FOR FEEDBACK  
**Date:** Thursday, October 10, 2013 6:49:47 PM  
**Attachments:** Responses to reviewers 101013.docx  
Jackie LeVan Manuscript NRN 10-10-13.docx  
Survey re Jackie LeVan's paper SUPPORT 10-10-13.docx

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Dear Colleagues:

Since both reviewers from Journal of Pediatrics ask for a (b)(4), (b)(6)

(b)(4), (b)(6) include one for your review. Please give me your feedback about this tentative survey. If this survey (or any edited version) is approved by you and all involved committees I will go forward, analyze the results and include it in the manuscript.

I attach a preliminary draft of an itemized response to Editors and Reviewers and a draft revised manuscript for your review.

I asked Lisa Wraga to respond to the reviewers' questions; updated results will be included in the next version.

Thank you for your collaboration.

Best regards,

Luc

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

**From:** ees.jpeds.0.2458cb.854b3616@eesmail.elsevier.com  
[\[mailto:ees.jpeds.0.2458cb.854b3616@eesmail.elsevier.com\]](mailto:ees.jpeds.0.2458cb.854b3616@eesmail.elsevier.com) On Behalf Of Journal Office  
**Sent:** Friday, October 04, 2013 12:12 PM  
**To:** Luc Brion; lucbrion@gmail.com  
**Subject:** Your Manuscript # 20131573 submitted to JPediatr

Ref: Ms. No. 20131573

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial The Journal of Pediatrics

Dear Dr. Brion,

Your manuscript has been evaluated by the Editors and independent reviewers whom we consider to be experts in the field. The manuscript was not accepted for publication in its current form. However, we will review a revised version that satisfactorily addresses editorial criteria, issues raised in this letter, and comments of the reviewers, which are appended below. We cannot guarantee, even with revision, that the manuscript will achieve a high enough priority for publication.

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text. Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (<http://www.jpeds.com/authorinfo>). Please upload the list of Study Group members as a separate Appendix file.

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi. Figure legends must appear on a separate page from the figures.

Online only tables and figures, if any, should be submitted "as usual" through EES. Indicate what should be

published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental."

Include with your revision a cover letter listing your responses to the comments from the Editors, as well as those from the reviewers (appended below). Detail the changes made to satisfy each comment or, if you do not agree with a criticism, include a rebuttal. Further consideration will be possible only if you send point-by-point responses to the reviewers and the Editors; changes should not be tracked or highlighted in the manuscript.

Please submit your revision within three months of the date of this letter. To submit a revision, go to <http://ees.elsevier.com/jped> and log in as an Author. Your submission record can be found by clicking on "Submissions Needing Revision."

Thank you for submitting your paper to The Journal of Pediatrics. We look forward to receiving your revision.

Sincerely,

Clyde J Wright, MD  
Associate Editor

William F. Balistreri, M.D.  
Editor

/rwl

Reviewers' comments:

Reviewer #1: (b)(4),(b)(5),(b)(6)

(b)(4),(b)(5),(b)(6)

Page 0833 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

Page 0834 of 2000

Withheld pursuant to exemption

(b)(4),(b)(5),(b)(6)

of the Freedom of Information and Privacy Act

(b)(4),(b)(5),(b)(6)

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**UT Southwestern Medical Center**  
The future of medicine, today.

**Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

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Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
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No reprints needed

**First draft:** Dr LeVan wrote the first draft of the manuscript.

**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

**Funding source:** NICHD

**Financial Statement:** No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

**Conflict of Interest Statement:** There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

**Clinical Trial registration:** NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 197250 words  
Article length: 2,41069774 words  
Revised 109/108713/13

List of Abbreviations:

ARR, Absolute risk reduction;

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## Abstract

### Objective

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to test the hypothesis that DR intubation decreased by 15% after compare medical care practices and neonatal outcomes before and after publication of SUPPORT withiwithin NICUs in NRN centers.

### Study Design:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. ~~The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.~~

### Results:

~~After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)~~

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

### **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if ~~publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR, decreased~~ changed after SUPPORT in centers that participated in the trial. We hypothesized that after SUPPORT there would be a 15% decrease ~~lower proportion of in~~ ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT, using a conservative estimate based on preliminary data at Parkland Memorial Hospital. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. ~~The most important neonatal outcomes were se included~~ the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. ~~We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes~~ changed after SUPPORT.

## Methods

### Study Design

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the

SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. The GDB has defined variables with detailed definitions; all patients are followed in GDB to ascertain all listed outcomes. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar numbers of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar ~~but not identical~~ to those used in SUPPORT, <sup>1,2</sup> however they were not identical because of specific variables and definitions listed in GDB at each period. Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was a practice variable, i.e., ETI in DR.

The most important sSecondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. Additional secondary outcomes included death by 36 weeks, BPD at 36 weeks, severe ROP at discharge, death or mechanical ventilation on day 7, and days on ventilators in survivors until discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of

bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR practice outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

#### Survey of center practices

We conducted a survey of center practices in the delivery room and the NICU (Table 1-Online only) to assess whether changes took place between the two epochs that were based on evidence other than that produced by SUPPORT.

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#### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain

differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>46</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes  $> 24$  hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>5-137-146</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

Sample size analysis:

In 1993-1997 the intubation rate among extremely low birth weight infants in the NRN was 80%.<sup>14</sup> Based on available GDB data when the study was designed, a first 2-year cohort and a second 3-year cohort were expected to each yield approximately 2400 neonates in the 11 centers. This sample size was sufficient for detecting a 15% relative

risk reduction in ETI from 80% to 68% with an alpha error less than 5% and a power greater than 99%, even if more than 50% of the patients met exclusion criteria. The sample size was large enough to conduct multivariate analysis with 10 patients per covariate.

### **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). ~~Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study, and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a~~ total study population included of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group. The baseline maternal and neonatal characteristics of both groups are shown in Table 24. There was more antenatal steroid use (~~89.6% vs. 82.8%, p<0.0001~~), maternal hypertension (~~27.4% vs. 19.9%, p<0.0001~~), maternal diabetes (~~5.4% vs. 2.6%, p<0.0001~~), cesarean section delivery (~~66.3% vs. 62.1%, p=0.0078~~), and less prolonged rupture of membranes (~~24.1% vs. 27.5%, p=0.017~~) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 32). The adjusted risk of DR

ETI (~~adjusted RR 0.88, 95% CI 0.85-0.91~~) significantly decreased after publication of SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 32). The adjusted risk of BPD/death (~~adjusted RR 0.94, 95% CI 0.89-0.99~~), severe ROP/death (~~adjusted RR 0.81, 95% CI 0.73-0.89~~), and death before discharge, (~~adjusted RR 0.86, 95% CI 0.76-0.98~~) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP, (~~adjusted RR 0.63, 95% CI 0.52-0.77~~) and of death or mechanical ventilation at day of life seven (~~adjusted RR 0.90, 95% CI 0.84-0.97~~) were significantly lower in the post-SUPPORT group (Table 32). In contrast, the adjusted risk of BPD (~~adjusted RR 1.04, 95% CI 0.97-1.1~~) and of death at 36 weeks (~~adjusted RR 0.88, 95% CI 0.76-1.00~~) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in Table 4, online only, ~~the appendix~~. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p=0.18$ ).

#### Discussion:

Infants 24<sup>0:7</sup> to 27<sup>6:7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI compared to those infants born before the initiation of the SUPPORT. ~~In the current study, the absolute risk reduction (ARR) in DR ETI between the two epochs spanning 2003-2012 (12%) was four times as large as the ARR in DR ETI observed in very low birth weight infants in the Vermont Oxford Network over a 10-year span between 2000 and 2009 (3.7%; 95% CI 4.2% to 3.3%).<sup>18</sup> The ARR over a 10-year span in the NRN and Vermont Oxford Network was less than that resulting from randomization to the CPAP arm versus the intubation arm during SUPPORT (59%).~~ In this study we compared data before SUPPORT with data after SUPPORT and did not ~~thus we were unable to analyze serial changes in -whether the decrease in proportion of ETI in each participating centers. The proportion of ETI in each center could have decreased -with increasing experience with took place at the time of introduction of and increasing experience with T-piece connectors before, during or after participation in -conduction of the Feasibility Trial (which took place during the first epoch, July 2002 to January 2003),<sup>15</sup> during participation the trial, or after~~ publication of the results of SUPPORT. The proportion of ETI in at ~~Parkland Memorial Hospital~~, one of the centers participating in SUPPORT, decreased in non-enrolled patients from baseline before SUPPORT (2003-2005) to epochs during SUPPORT (2005-2009) and before its publication (2009-2010);<sup>17</sup> ETI in a subset of these patients decreased more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network (2003-2004 versus 2006-2009).<sup>16</sup> In another NRN center which participated in SUPPORT, the proportion of ETI decreased after introduction of bubble CPAP in 2000, i.e., before SUPPORT.<sup>17</sup> The fact that 5 centers had participated in

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~~the Feasibility Trial may have limited the overall decrease in DR ETI observed in this study; Lack of correlation between We had hypothesized that the change in the proportion in ETI after SUPPORT and would be greater in centers with high-baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study and from the narrow range (82-97%) of and from the fact that 9 of the 11 centers had pre-SUPPORT proportions of ETI in 9 of 11 centers that varied within a narrow range of about 82-97%.,~~  
~~and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD-NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.~~

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods, the use of inclusion and exclusion criteria that were similar to resembled (though

~~did not exactly match) those used in SUPPORT, and the inclusion of . We were able to analyze center specific changes after SUPPORT as well as changes in the entire sample, because we only used We elected to limit for this study to centers that remained in the NICHD NRN during the two cohorts, thereby limiting bias due to 1, because of Large inter-institutional differences that have been observed in previous NRN studies; this allowed us to analyze center specific changes after SUPPORT as well as changes in the entire sample. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center specific changes after SUPPORT as well as changes in the entire sample.~~

However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, strict selection criteria to high percentage of exclusions, the limited number of variables included in the GDB, and secular trends, and lack of information in the . Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those

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~~used in the primary outcomes of SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication;<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB on did not include information on individual use of DR CPAP, oxygen saturation targets in the DR or the NICU, or the rationale used for each various practice, s used for each patient in each center. It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results.~~

~~Since we did not adjust p value for multiple comparisons, secondary and tertiary variables should all be considered as exploratory. Mortality The risk of death before discharge was significantly decreased in the group of infants in the post-SUPPORT group. This finding contrasts with previous published reports from the NICHD NRN; which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002;<sup>49</sup> and between 2003 and 2007.<sup>18,19,20</sup> but it is~~

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~~consistent with a recent review a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality among extremely low birthweight infants enrolled in the GDB between 2000-2003 and 2008-2011.<sup>20</sup> Similarly, mortality in very low birth weight infants decreased in the Vermont Oxford Network between 2000 and 2009.<sup>21,21</sup>~~

~~This study was not designed to test whether any change in secondary or tertiary variables were associated with changes in O2 saturation or with the application in practice of evidence from SUPPORT. Since the risk for death or BPD and death or ROP was not affected by randomization in SUPPORT, the decreased risk observed after SUPPORT may be related to practice changes based on evidence from other studies.~~

~~We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since serial oxygen saturation measurements were not prospectively collected in the GDB before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Several center-specific practice guidelines and policies individual practice may have changed between the two epochs, based on new information on other studies rather than SUPPORT, e.g., antenatal DR studies on and NICU management and outcomes antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive pressure ventilation,<sup>26</sup> prevention of central line-associated~~

bloodstream infections,<sup>27,28</sup> or nutrition.<sup>22-31,29,29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>200</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies.

This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have developed experience with T-piece connectors during SUPPORT and with tight oxygen monitoring and thus might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge in for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial

compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or death of mechanical ventilation in days seven of life also

was significantly lower in our study. The risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact

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~~that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.~~

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**Acknowledgments:**

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**Jaclyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Luc P Brion:** Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

**Lisa Wrage:** Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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**Waldemar A. Carlo:** Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011);

Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, BA RN; Arlene Zadell RN; Julie DiFiore, BS.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD.

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The eleven NRN centers that remained in the NICHD NRN during the duration of this study included: Brown University; Case Western Reserve University; Cincinnati Children's Hospital Medical Center; Duke University; Emory University; Indiana University; Stanford University; University of Alabama at Birmingham; University of Texas Health Science Center at Houston; University of Texas Southwestern Medical Center; Wayne State University.

Preliminary data were presented as a poster. Levan J, Brion LP, Wrage LA, on behalf of the NICHD NRN. Changes in therapy and outcomes associated with the SUPPORT Trial. Poster presentation at the Pediatric Academy Society Meeting, Washington DC, May 5, 2013; E-PAS2013:2924.474

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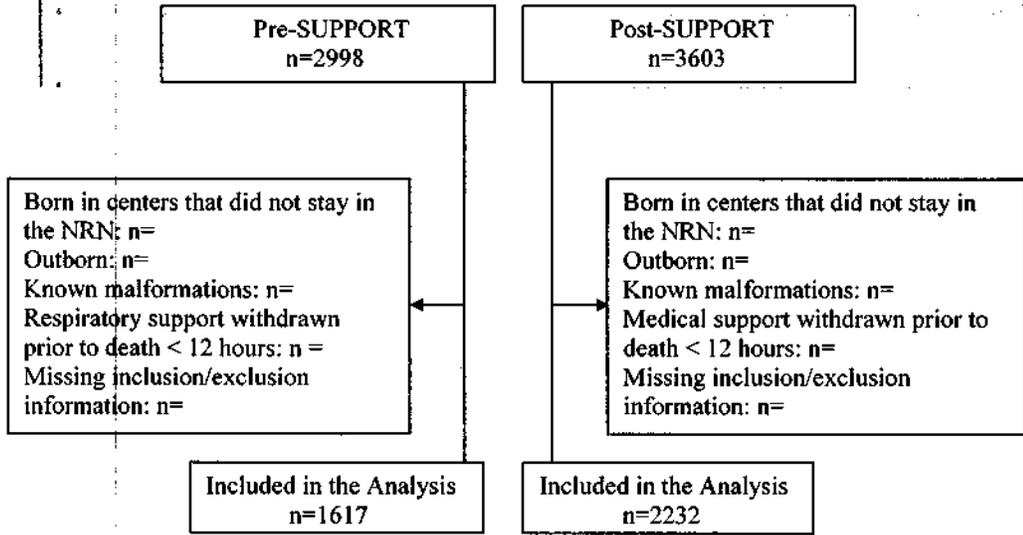
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**Figure Legends**

**Figure 1. Flow diagram**

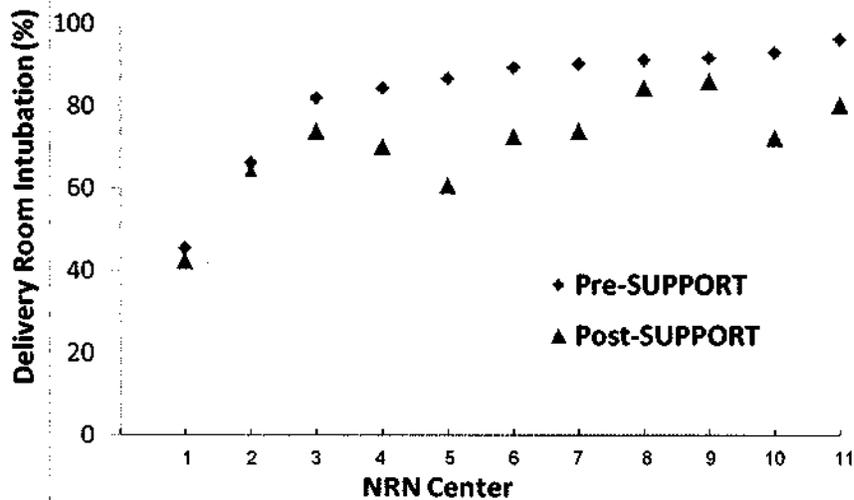
**Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study**

Figure 1



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**Figure 2**



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**Table 1 – Online only**  
**Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial**  
 Survey - Table of Confounding Variables

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	1/3-1/5			7/12-6/14		
	Details of Intervention	Indication	Policy (P)/ Guideline (G)	Details of Intervention	Indication	Policy (P)/ Guideline (G)
<u>Prenatal Steroids</u>						
<u>Intrapartum Magnesium use for neuroprotection</u>						
<u>Magnesium use for preeclampsia</u>						
<u>DR cardiac massage or medications</u>						
<u>T piece resuscitators in DR</u>						
<u>Use of CPAP in DR</u>						
<u>Use of PEEP in DR</u>						
<u>Starting FIO2 in DR</u>						
<u>Use of preductal pulse oximeter in DR to adjust FIO2</u>						
<u>Saturation goals in DR</u>						
<u>Temperature control in DR</u>						
<u>Golden hour upon NICU admission</u>						
<u>Postnatal O2 saturation target range in NICU</u>						

<u>Postnatal O2 saturation lower and upper limits in NICU</u>						
<u>Adjustment of oxygen administration for procedures</u>						
<u>Surfactant administration</u>						
<u>Vitamin A prophylaxis</u>						
<u>Caffeine</u>						
<u>Prophylactic indomethacin or ibuprofen</u>						
<u>Physiologic testing for BPD</u>						
<u>Postnatal Steroids</u>						
<u>PDA medical closure</u>						
<u>PDA surgical closure</u>						

**Table 2. Maternal and Neonatal Characteristics<sup>1</sup>**

<u>Characteristic</u>	<u>Pre-SUPPORT N=1617</u>	<u>Post-SUPPORT N=2232</u>	<u>p-value<sup>2</sup></u>
<u>Birth weight (grams)</u>	<u>825 (191)</u>	<u>818 (194)</u>	<u>0.32</u>
<u>GA (weeks)</u>	<u>25.7 (1.1)</u>	<u>25.7 (1.1)</u>	<u>0.93</u>
<u>Male</u>	<u>858/1617 (53.1)</u>	<u>1126/2232 (50.5)</u>	<u>0.11</u>
<u>Race/ethnicity:</u>			
<u>Non-Hispanic Black</u>	<u>727/1617 (45.0)</u>	<u>965/2192 (44.0)</u>	<u>0.02</u>
<u>Non-Hispanic White</u>	<u>603/1617 (37.3)</u>	<u>808/2192 (36.9)</u>	
<u>Hispanic</u>	<u>241/1617 (14.9)</u>	<u>314/2192 (14.3)</u>	
<u>Other</u>	<u>46/1617 (2.8)</u>	<u>105/2192 (4.8)</u>	
<u>Antenatal Steroids: any type</u>	<u>1338/1616 (82.8)</u>	<u>1994/2225 (89.6)</u>	<u>&lt;.0001</u>
<u>Antenatal Steroids: betamethasone</u>	<u>953/1614 (59.1)</u>	<u>1980/2229 (88.8)</u>	<u>&lt;.0001</u>
<u>Multiple birth</u>	<u>370/1617 (22.9)</u>	<u>540/2228 (24.2)</u>	<u>0.33</u>
<u>Mode of delivery: cesarean section</u>	<u>1004/1617 (62.1)</u>	<u>1476/2228 (66.3)</u>	<u>0.008</u>
<u>Prolonged rupture of membranes: (&gt; 24 hours)</u>	<u>436/1586 (27.5)</u>	<u>520/2161 (24.1)</u>	<u>0.017</u>
<u>Maternal hypertension</u>	<u>322/1617 (19.9)</u>	<u>610/2230 (27.4)</u>	<u>&lt;.0001</u>
<u>Maternal diabetes</u>	<u>42/1617 (2.6)</u>	<u>120/2231 (5.4)</u>	<u>&lt;.0001</u>
<u>Maternal Antibiotics</u>	<u>1198/1615 (74.2)</u>	<u>1618/2228 (72.6)</u>	<u>0.28</u>

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Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup> The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 3. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>4</sup></b>
<b>Intubated in delivery room (primary outcome)</b>	<b>1313/1617 (81.2)</b>	<b>1539/2232 (69.0)</b>	<b>&lt;0.0001</b>		<b>0.88 (0.85-0.91)</b>	<b>&lt;0.0001</b>
<b>BPD or death at 36 weeks</b>	<b>970/1617 (60.0)</b>	<b>1199/2213 (54.2)</b>	<b>0.0003</b>	<b>=</b>	<b>0.94 (0.89-0.99)</b>	<b>0.02</b>
<b>Severe ROP or death</b>	<b>515/1581 (32.6)</b>	<b>559/2165 (25.8)</b>	<b>&lt;0.0001</b>	<b>=</b>	<b>0.81 (0.73-0.89)</b>	<b>&lt;0.0001</b>
<b>Death before discharge</b>	<b>358/1614 (22.2)</b>	<b>393/2196 (17.9)</b>	<b>0.001</b>	<b>=</b>	<b>0.86 (0.76-0.98)</b>	<b>0.02</b>
<b>Bronchopulmonary dysplasia (36 weeks)</b>	<b>664/1311 (50.7)</b>	<b>855/1869 (45.8)</b>	<b>0.0064</b>	<b>=</b>	<b>1.04 (0.97-1.1)</b>	<b>0.26</b>
<b>Severe ROP by discharge</b>	<b>174/1294 (13.5)</b>	<b>181/1873 (9.7)</b>	<b>0.0009</b>	<b>=</b>	<b>0.63 (0.52-0.77)</b>	<b>&lt;0.0001</b>
<b>Death by 36 weeks</b>	<b>306/1617 (18.9)</b>	<b>344/2222 (15.5)</b>	<b>0.0050</b>	<b>=</b>	<b>0.88 (0.76-1.00)</b>	<b>0.06</b>
<b>Death or mechanical ventilation on day 7</b>	<b>741/1613 (45.9)</b>	<b>875/2211 (39.6)</b>	<b>&lt;0.0001</b>	<b>=</b>	<b>0.90 (0.84-0.97)</b>	<b>0.003</b>
<b>Days on ventilator (survivors) until discharge</b>	<b>22.3 (24.4), 13</b>	<b>17.8 (21.3), 9.0</b>	<b>&lt;0.0001</b>	<b>-4.7 (-6.1, -3.2)</b>		<b>&lt;0.0001</b>

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA,

patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO2 at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 4- Online only. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604/1617 (99.2)	2167/2232(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123/1617 (7.6)	173/2232 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89/1617 (5.5)	84/2232 (3.8)	0.010
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.003
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427/1617 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14/1617 (0.9)	29/2232 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.003
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177/1617 (11.0)	209/2232 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup>presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD), median for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

**Changes in Therapy and Outcomes in 24-27<sup>6/7</sup> week GA infants Associated with The SUPPORT Trial Survey - Table of Confounding Variables, 10/10/13**

	1/3-1/5			7/12-6/14		
	Details of Intervention	Indication	Policy (P)/ Guideline (G)	Details of Intervention	Indication	Policy (P)/ Guideline (G)
Prenatal Steroids						
Intrapartum Magnesium use for neuroprotection						
Magnesium use for preeclampsia						
DR cardiac massage or medications						
T piece resuscitators in DR						
Use of CPAP in DR						
Use of PEEP in DR						
Starting FiO2 in DR						
Use of preductal pulse oximeter in DR to adjust FiO2						
Saturation goals in DR						
Temperature control in DR						
Golden hour upon NICU admission						
Postnatal O2 saturation target range in NICU						
Postnatal O2 saturation lower and upper limits in NICU						
Adjustment of oxygen administration for procedures						
Surfactant administration						
Vitamin A prophylaxis						

Caffeine						
Prophylactic indomethacin or ibuprofen						
Physiologic testing for BPD						
Postnatal Steroids						
PDA medical closure						
PDA surgical closure						

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Thursday, October 10, 2013 1:00 PM  
**To:** Jarman, John (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions for NIH

Thanks. And I sent out query that is resulting in other contacts for renate to use.

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

**From:** Jarman, John (NIH/NICHD) [E]  
**Sent:** Thursday, October 10, 2013 12:59 PM  
**To:** Hudson, Kathy (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions for NIH

See the following note from Cathy Spong:

(b)(6) would be best but he (b)(5)

Michelle Walsh at case western her 2168443759. [Mcw3@cwru.edu](mailto:Mcw3@cwru.edu)

Abbott laptook at brown  
4012741122 ext 7421  
Email [alaptook@wihri.org](mailto:alaptook@wihri.org)

Catherine Y Spong MD  
Associate Director for Extramural Research Director, Division of Extramural Research NICHD, NIH  
6100 Executive Blvd Rm 4A05A Bethesda MD 20892 [SpongC@mail.nih.gov](mailto:SpongC@mail.nih.gov) Phone 301 435 6894

John S. Jarman  
Associate Director for Administration/Executive Officer Eunice Kennedy Shriver  
National Institute of Child Health and Human Development  
National Institutes of Health, DHHS  
301-496-0648

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

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Thursday, October 10, 2013 10:52 AM  
**To:** Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Jarman, John (NIH/NICHD) [E]  
**Subject:** RE: Additional SUPPORT study questions for NIH

Okay. thanks. Let's see if we can (b)(5)

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

From: Myles, Renate (NIH/OD) [E]  
Sent: Thursday, October 10, 2013 10:45 AM  
To: Hudson, Kathy (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Jarman, John (NIH/NICHD) [E]  
Subject: RE: Additional SUPPORT study questions for NIH

This is the producer for Sharyl Attkisson on CBS Sunday Morning that covered the HHS public meeting and interviewed both Jerry and Alan at the meeting. We had been working with her for several weeks which included setting up a background call with Rose Higgins to clarify some points. (b)(5)

(b)(5)

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

From: Hudson, Kathy (NIH/OD) [E]  
Sent: Thursday, October 10, 2013 10:41 AM  
To: Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Jarman, John (NIH/NICHD) [E]  
Subject: RE: Additional SUPPORT study questions for NIH

Looping in Alan and John Jarman from NICHD to see if we can get help on how to proceed.

Renate. (b)(5)

(b)(5)

Alan, is there someone in the NRN we could send the reporter to?

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

From: Myles, Renate (NIH/OD) [E]  
Sent: Thursday, October 10, 2013 10:33 AM  
To: Hudson, Kathy (NIH/OD) [E]; Burklow, John (NIH/OD) [E]  
Subject: FW: Additional SUPPORT study questions for NIH

Heads up (b)(5)

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

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Thursday, October 10, 2013 10:30 AM  
To: Myles, Renate (NIH/OD) [E]  
Subject: Additional SUPPORT study questions for NIH

Hi Renate,

We're trying to clarify a few points for our story on the SUPPORT study. Here are our questions:

1. Did the treating doctors, nurses and other clinicians know:
  - a. which babies were in the study?
  - b. that the oxygen monitors were altered?

2. And if they did know that the oxygen monitors were altered, did they know any details of how they were altered (and if so, what were they told?) 3. What instructions or guidance were the clinicians given in handling the babies that had the altered monitors?

Please provide a response as soon as possible. Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Walsh, Michele  
**To:** Cunningham, Meg  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)  
**Date:** Tuesday, October 01, 2013 12:18:02 PM

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I would also like to report the MRP outcomes- 15 minutes?

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu  
Phone: (216) 844-3387  
Fax: (216) 844-3380

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**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Tuesday, October 01, 2013 11:43 AM  
**To:** Walsh, Michele  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; srhintz@stanford.edu; Newman, Jamie; Das, Abhik; Zaterka-Baxter, Kristin  
**Subject:** RE: Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)

We have some extra time on the agenda that Susan can use for this.

Thanks,  
Meg

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**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, October 01, 2013 11:07 AM  
**To:** Cunningham, Meg  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Susan Hintz (srhintz@stanford.edu)  
**Subject:** RE: Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)

My only thought: I am hearing many rumors about multiple secondaries to School age: and I would like to understand exactly what the children are going Through: Lots of samples, and procedures beyond imaging and follow up testing. I must have missed the boat on this! Or we approved them so long ago, and in Pieces so that the combined impact was not appreciated... or it is just my Half-heimers Progressing!

I wonder if Susan could summarize all procedures and secondaries at the Steering committee?

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu

Phone: (216) 844-3387

Fax: (216) 844-3380

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**From:** Cunningham, Meg [<mailto:mcunningham@rti.org>]  
**Sent:** Tuesday, October 01, 2013 10:35 AM  
**To:** [alaptook@WIHL.org](mailto:alaptook@WIHL.org); Bradley Yoder; [adas@rti.org](mailto:adas@rti.org); Higgins, Rosemary (NIH/NICHD) [E]; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [MPeralta@PEDS.UAB.EDU](mailto:MPeralta@PEDS.UAB.EDU); nancy newman; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); Wallace, Dennis; Wally Carlo, M.D.; [wrich@ucsd.edu](mailto:wrich@ucsd.edu); Yvonne Vaucher  
**Cc:** [sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu); Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeel; Brenda Vecchio; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin  
**Subject:** RE: Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)

Hi All,

This call was scheduled in error. We originally intended to schedule a SUPPORT School Age call, but scheduled a SUPPORT call instead.

Please let me know if you think this call is needed by the end of the day. If so, we will have this call tomorrow. If there is nothing to discuss, we can cancel.

Thanks,

Meg

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**From:** Lewis-Evans, Amanda  
**Sent:** Wednesday, September 11, 2013 1:37 PM  
**To:** Abbot Laptok ([alaptook@WIHL.org](mailto:alaptook@WIHL.org)); Bradley Yoder; Das, Abhik ([adas@rti.org](mailto:adas@rti.org)); 'Higgins, Rosemary (NIH/NICHD) [E]'; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [MPeralta@PEDS.UAB.EDU](mailto:MPeralta@PEDS.UAB.EDU); nancy newman; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); Wallace, Dennis; Wally Carlo, M.D.; [wrich@ucsd.edu](mailto:wrich@ucsd.edu); Yvonne Vaucher  
**Cc:** ([sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu)); 'Archer, Stephanie (NIH/NICHD) [E]'; Becky Brazeel; 'Brenda Vecchio'; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin  
**Subject:** Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)

Dear all,

The Support Subcommittee Call has been scheduled for:

**Wednesday, 10/2  
11:00 AM ET**

Dial:  
Within the USA  
**866-675-3256**

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we were unable to find a time that worked with everyone's schedule, so Betty Vohr will be unable to attend.

Thanks,

Amanda

**From:** Lewis-Evans, Amanda

**Sent:** Tuesday, August 27, 2013 2:22 PM

**To:** [SCRN] Stoll, Barbara ([barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu)); Bell, Edward; Das, Abhik ([adas@rti.org](mailto:adas@rti.org)); 'dstevenson@stanford.edu'; Gantz, Marie ([mgantz@rti.org](mailto:mgantz@rti.org)); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); 'Higgins, Rosemary (NIH/NICHD) [E]'; [jeff-murray@uiowa.edu](mailto:jeff-murray@uiowa.edu); [john-dagle@uiowa.edu](mailto:john-dagle@uiowa.edu); Johnson, Karen; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); McDonald, Scott A.; 'Michael Cotten'; Namasivayam Ambalavanan ([nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu)); Page, Grier; 'Sood, Beena'; [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wallace, Dennis; Whitehead, Nedra; Bill Truog; Leif Nelin; Pablo Sanchez ([pablo.sanchez@nationwidechildrens.org](mailto:pablo.sanchez@nationwidechildrens.org)); Uday Devaskar; Wally Carlo, M.D.; Anna Maria Hibbs; Brenda Polindexter ([bpolindex@iu.edu](mailto:bpolindex@iu.edu)); [byohr@wihri.org](mailto:byohr@wihri.org); DeMauro, Sara M; 'Kathleen.A.Kennedy@uth.tmc.edu'; Leslie Dawn Wilson ([ldw@iu.edu](mailto:ldw@iu.edu)); Tarah Colaizy; Wrage, Lisa Ann; Andi Duncan; Cheri Gauldin; 'Conra Lacy'; 'Erika Fernandez'; Greg Sokol ([gsokol@iu.edu](mailto:gsokol@iu.edu)); Kendrick, Douglas E. (in StatEpi); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); Maky Fraga; [mcw3@cwru.edu](mailto:mcw3@cwru.edu); Sandra Beauman; Abbot Laptook ([alaptook@WIHRI.org](mailto:alaptook@WIHRI.org)); Bethany Ball; [ellen\\_hale@oz.ped.emory.edu](mailto:ellen_hale@oz.ped.emory.edu); nancy newman; 'sshankar@med.wayne.edu'; Ann Marie Scorsone; Bob Ward ([Robert.Ward@hsc.utah.edu](mailto:Robert.Ward@hsc.utah.edu)); Carol Cole; [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); Nolen, Tracy; Williams, Rick L.; [wph@wihri.org](mailto:wph@wihri.org); Zaterka-Baxter, Kristin; [apappas@med.wayne.edu](mailto:apappas@med.wayne.edu); Cathy Grisby ([cathy.grisby@uc.edu](mailto:cathy.grisby@uc.edu)); 'claudia.pedroza@uth.tmc.edu'; [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); [rbara@med.wayne.edu](mailto:rbara@med.wayne.edu); [Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu); Aasma Chaudhary; [ahensman@wihri.org](mailto:ahensman@wihri.org); Huitema, Carolyn Petrie; Munoz, Breda; Bradley Yoder; Diana Vasili; Eggleston, Barry; Joanna Beachy; Kevin Dysart; 'Matt Laughon'; [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); 'Georgia.E.McDavid@uth.tmc.edu'; Kevin Lally ([Kevin.P.Lally@uth.tmc.edu](mailto:Kevin.P.Lally@uth.tmc.edu)); Marty Blakely; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [srhintz@stanford.edu](mailto:srhintz@stanford.edu); Gerry Taylor; Hammond, Jane ([hammond@rti.org](mailto:hammond@rti.org)); Jean Lowe; Maureen Hack ([mxh7@cwru.edu](mailto:mxh7@cwru.edu)); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)

**Cc:** 'Lewis-Evans, Amanda ([alewis@rti.org](mailto:alewis@rti.org))'; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin; ([debra.camputaro@yale.edu](mailto:debra.camputaro@yale.edu)); ([pamela.neville@duke.edu](mailto:pamela.neville@duke.edu)); 'Archer, Stephanie (NIH/NICHD) [E]'; [ganza025@mc.duke.edu](mailto:ganza025@mc.duke.edu); [jwaidne@emory.edu](mailto:jwaidne@emory.edu); [lisa.joo@stanford.edu](mailto:lisa.joo@stanford.edu); Sarah Barten; Becky Brazeel; Kristie Smiley; Garcia, Deborah; [rrapozafarrands@wihri.org](mailto:rrapozafarrands@wihri.org); Cunningham, Meg ([mcunningham@rti.org](mailto:mcunningham@rti.org)); Lewis-Evans, Amanda; Zaterka-Baxter, Kristin ([kzaterka@rti.org](mailto:kzaterka@rti.org)); 'Brenda Vecchio'; [lmoores@med.wayne.edu](mailto:lmoores@med.wayne.edu); ([sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu)); Linda Mathieu; Michelle Smith ([Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu)); Matthew Seckman; Robin Brown; Scottie Wahlstrom; Auman, Jeanette O.; Newman, Jamie; Suzanne Sayers

**Subject:** NRN Subcommittee Calls - Availability Request

Dear all,

We would like to schedule calls prior to the October SCM for the following subcommittees:

Genomics

Publications

MILK

Term and Late Preterm Hypotension

INS  
GDB  
OC  
Late Hypothermia  
Premie Hypothermia  
NEST  
SUPPORT Neuro School Age

Please provide your availability for the following dates via email or using the **THREE** separate Doodle polls:

**PART 1:** <http://doodle.com/b33f5anfux2ynews>

9/3, Tu  
9/4, W  
9/5, Th  
9/6, F

9/9, M  
9/10, Tu  
9/11, W  
9/12, Th  
9/13, F

**PART 2:** <http://doodle.com/r4eprd2hh8udkhbe>

9/16, M  
9/17, Tu  
9/18, W  
9/19, Th  
9/20, F

9/23, M  
9/24, Tu  
9/25, W  
9/26, Th  
9/27, F

9/30, M

**PART 3:** <http://doodle.com/psbrys3r5epfn52b>

10/1, Tu  
10/2, W  
10/3, Th  
10/4, F

10/7, M  
10/8, Tu  
10/9, W  
10/10, Th  
10/11, F

Thanks,

Amanda Lewis-Evans  
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3040 Cornwallis Road  
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Federal and Ohio law protect patient medical information, including psychiatric disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT papers  
**Date:** Friday, September 27, 2013 2:55:59 PM

Thanks Rose and Stephanie  
Carol

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 02:27 PM Eastern Standard Time  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: SUPPORT papers

Given the high profile of the SUPPORT Trial, we will keep you posted on the publications. We will also have our press folks assist at NICHD.  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 2:11 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT papers

Hi Carol,

Just to keep you in the loop about recent and upcoming SUPPORT publications, attached are 3 upcoming papers:

- Kennedy KA; et al. Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants. This paper was recently resubmitted to the Journal of Perinatology
- LeVan J; et al. Changes in Therapy and Outcomes Associated with the SUPPORT Trial. Pediatrics recently rejected this paper; the plan is to submit it to Journal of Pediatrics next.
- Stevens TP; et al. Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial. Pediatrics recently rejected this paper; the plan is to submit it to Journal of Pediatrics next.

In addition, Jean Lowe's paper was recently published in Early Human Development:

- Lowe JR; et al. [Early working memory as a racially and ethnically neutral measure of outcome in extremely preterm children at 18-22 months.](#)

Below is the current list of upcoming SUPPORT papers (those that say "Reviewing" are being reviewed or have recently been reviewed by the NRN Publications Subcommittee, but not yet submitted a journal); Revising means it was submitted and rejected by at least one journal and is in preparation for resubmission).

Stephanie

Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
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Rockville, MD 20852

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Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

SUPPORT papers pending:

Current Status	Authors	Paper Working Title	Comments
1 Pending	Gantz MG; Creel D; Rich W; Higgins RD; Das A	Enrollment propensity weighting to assess the generalizability of a randomized clinical trial	11/30/11 Submitted abst. to Society of Clinical Trials 2/7/12 Accepted by SCT for poster presentation 5/8/12 MG: Drafting

			7/11/12 MG: Revising 3/8/13 MG: I am in the process of responding to comments made by Abhik. I hope to have a new draft to circulate by the end of the month.
1. Pending	Hintz SR; Bulas D; Slovis TL; Cheng H; Finer NN; Das A; Higgins RD; for the SUPPORT Subcommittee and NICHD Neonatal Research Network	Serial cranial US and near term brain MRI findings of extremely preterm infants in the SUPPORT NEURO cohort	5/1/10 Late Breaker Abstract for PAS 10/15/10 SH: Additional analysis and 3rd central reader adjudication completed; working on paper 12/26/10 SH: requires additional data analysis 3/7/11 SH: Waiting for final tables from Cheng at RTI. Analysis should be complete in next 2 weeks. 3/30/11 SH: Adjudication completed 8/2010; additional analysis completed 3/2011; paper being drafted. 6/2/11 SH: Manuscript drafts in process 11/23/11 SH: Working on MRI descriptive paper first, then reorganizing CUS paper to include FU. 1/17/12 SH: Reworking to include FU because I do not think another CUS descriptive findings paper will be of interest to the readership. 7/6/12 SH: Combining with MRI paper 7/5/13 SH: Estimated draft ready in September
1. Pending	Vaucher YE; Hintz SR; Rich W	Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?	11/15/12 Submitted for PAS 2013 2/11/13 PAS Accepted 5/1/13 Presented at PAS
2. Drafted	Gantz MG; Carlo WA; Finer NN; and the SUPPORT Subcommittee for the NICHD Neonatal Research Network	Oxygen saturations and retinopathy of extremely prematurity in preterm infants	5/1/11 Presented at PAS 2011 6/8/11 WC: Working on it 9/23/11 WC: Working on it 1/17/12 Drafted. Marie will take over a first author 5/8/12 MG: Revising 7/11/12 MG: Revising 3/8/13 MG: Have made substantial revisions and rerun the analysis on oximeter data using an improved smoothing method (although results did not change). I am close to sending it back to Wally for his review (that should happen in the next couple of weeks). 7/11/13 Sent to coauthors
2. Drafted	Hintz SR; Wraga LA; Barnes PD; Bulas D; Slovis T; Das A; Finer NN; Higgins RD; for the SUPPORT Subcommittee	Brain MRI and cranial US to predict 18-23 month neurodevelopmental outcomes in extremely preterm infants in the SUPPORT NEURO cohort	5/1/12 Presented at PAS 2012 7/6/12 SH: Being written 7/5/13 SH: Estimated draft ready in September 9/11/13 Draft sent to coauthors
2. Drafted	Navarrete CT; Duara S; on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network	Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth	5/1/12 Presented at PAS 2012 7/6/12 CTN: Waiting on some additional analyses before I can complete the first draft of the manuscript. 3/8/13 SWA requested update 7/5/13 SWA requested update 7/11/13 Draft sent to RTI 7/12/13 Draft sent to SubC
3. Reviewing	Ambalavanan N; Carlo WA; Wraga LA; Das A; Laughon MM; Cotten CM; Kennedy KA; Luptook AR; Shankaran S; Walsh MC; Higgins RD	Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)	6/2/11 NA: Abstract not accepted at PAS. Manuscript in preparation 1/18/12 NA: Manuscript in preparation – will need additional analyses. 5/7/12 NA: Manuscript in preparation. 7/3/12 NA: Manuscript in preparation. 12/27/12 NA: Manuscript in preparation. 2/21/13 Draft sent to coauthors 7/5/13: Additional analysis done by RTI May 2013; Fourth draft sent to co-authors on 7/5/13 8/5/13 Sent to SUPPORT subC for review 9/23/13: NA: Two reviews received from Publication Subcommittee; additional reviews awaited and manuscript being revised.
4. Submitted	Kennedy KA; Wraga LA; Higgins RD; Finer NN; Carlo WA; Walsh MC; Luptook AR; Faix RG; Yoder B; Schibler KR; Gantz MG; Das A; Newman NS; Rich W; Phelps DL	Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants	5/1/12 Presented at PAS 2012 5/25/12 Draft sent to coauthors 7/30/12 Sent to SUPPORT Subcommittee 12/14/12 Submitted to Pubs 3/8/13 Delayed Pubs reviews; reviews sent to author 2/27/13 KK: plan to submit it to Pediatrics 3/19/13 3/19/13 Submitted to Peds 4/25/13 Peds rejected 6/6/13 Submitting to J Perinatology 6/13/13 J Perinatology rejected 7/18/13 Resubmitted to J Perinatology

5	Revising	LeVan J; Brion LP; Wraga LA; for the NICHD Neonatal Research Network	Changes in Therapy and Outcomes Associated with the SUPPORT Trial	11/15/12 Submitted for PAS 2013 2/11/13 PAS Accepted 6/24/13 Submitted to Peds 9/5/13 Peds rejected; will submit to Jpeds
5	Revising	Stevens TP; Finer NN; Carlo WA; Szilagyi PG; Walsh MC; Gantz MG; Laptook AR; Yoder BA; Faix RG; Newman JE; Das A; Do BT; Schibler K; Rich W; Newman NS; Ehrenkranz RA; Peralta-Carcelen M; Vohr BR; Wilson-Costello DE; Yolton K; Heyne RJ; Dusick AM; Evans PW; Vaucher YE; Adams-Chapman I; McGowan EC; Bodnar A; Pappas A; Hintz SR; Acarregul MJ; Fuller J; Goldstein RF; Bauer CR; O'Shea TM; Myers GI; Higgins RD	Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial	11/15/12 Submitted for PAS 2013 11/26/12 Manuscript submitted to Pubs 1/8/13 BT did not receive the manuscript in November; resent it 2/11/13 PAS Accepted 4/30/13 Peds rejected, but can resubmit with revisions 6/25/13 Revisions sent to coauthors 8/5/13 Peds rejected revisions; will try J Peds
		Lowe JR; Duncan AF; Bann CM; Fuller J; Hintz SR; Das A; Higgins RD; Watterberg KL; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network	Early working memory as a racially and ethnically neutral measure of outcome in extremely preterm children at 18-22 months	<a href="http://www.ncbi.nlm.nih.gov/pubmed/23993309">http://www.ncbi.nlm.nih.gov/pubmed/23993309</a> 5/1/12 Presented at PAS 2012 7/9/12 II - The manuscript is in preparation and we hope to submit in August. The first draft has been sent to the co-authors. 9/12/12 New version sent to coauthors for review 9/27/12 II - waiting on Carla Bann to edit the comments specific to statistics. 10/9/12 Submitted to Pubs 11/27/12 Submitted to J Peds 3/8/13 II - J Peds rejected; revising for resubmission 4/22/13 Submitted to JAMA Pediatrics 5/17/13 JAMA Peds rejected; submitted to Early Human Dev 8/7/13 Early Human Dev accepted 8/17/13 II submitted to NIHMS

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 11:26 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance

Yes

What has gone through recently??

Breathing outcomes and LeVan papers? Please send the drafts to Carol Blaisdell and copy me

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 11:25 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT paper clearance

Should these also go to NHLBI as an FYI?

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance  
**Date:** Friday, September 27, 2013 1:58:25 PM

I told her about all of them when I spoke to her – once accepted, we will re-remind her and Bob Bock

Thanks  
 Rose

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 Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
 Pregnancy and Perinatology Branch  
 NIH  
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 MSC 7510  
 Bethesda, MD 20892  
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 301-435-7909  
 301-496-5575  
 301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 1:58 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance

Should we let Mona know too? Not sure how aware she was of the other papers when they first came through clearance.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 1:53 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance

They knew about the Vaucher FU paper – can you send her Kennedy, LeVan and Stevens?

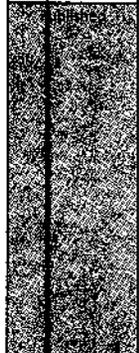
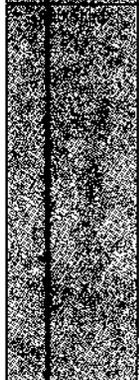
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 301-435-7909  
 301-496-5575  
 301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 11:35 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance

Here are all of the active SUPPORT papers in order of their status. I assume she received the SUPPORT FU paper, but not sure that she has seen any of the others that have been reviewed by Pubs (Ambal, Kennedy, LeVan, Stevens, Lowe)?

Current Status	Authors	Paper Working Title	Comments
Pending	Gantz MG, Creel D, Rich W, Higgins RD; Das A	Enrollment propensity weighting to assess the generalizability of a randomized clinical trial	11/30/11 Submitted abstr. to Society of Clinical Trials 2/7/12 Accepted by SCT for poster presentation 5/8/12 MG: Drafting 7/11/12 MG: Revising 3/8/13 MG: I am in the process of responding to comments made by Abhik. I hope to have a new draft to circulate by the end of the month.
Pending	Hintz SR; Bulas D; Slovis TL; Cheng H; Finer NN; Das A; Higgins RD; for the SUPPORT Subcommittee and NICHD Neonatal Research Network	Serial cranial US and near term brain MRI findings of extremely preterm infants in the SUPPORT/NEURO cohort	5/1/10 Late Breaker Abstract for PAS 10/15/10 SH: Additional analysis and 3rd central reader adjudication completed; working on paper 12/26/10 SH: requires additional data analysis 3/7/11 SH: Waiting for final tables from Cheng at RTI. Analysis should be complete in next 2 weeks.

			3/30/11 SH: Adjudication completed 8/2010; additional analysis completed 3/2011; paper being drafted. 6/2/11 SH: Manuscript drafts in process 11/23/11 SH: Working on MRI descriptive paper first, then reorganizing CUS paper to include FU. 1/17/12 SH: Reworking to include FU because I do not think another CUS descriptive findings paper will be of interest to the readership. 7/6/12 SH: Combining with MRI paper 7/5/13 SH: Estimated draft ready in September
1. Pending	Vaucher YE; Hintz SR; Rich W	Antenatal Enrollment in Clinical Trials: Is Neurodevelopmental Outcome Representative?	11/15/12 Submitted for PAS 2013 2/11/13 PAS Accepted 5/1/13 Presented at PAS
2. Drafted	Gantz MG; Carlo WA; Finer NN; and the SUPPORT Subcommittee for the NICHD Neonatal Research Network	Oxygen saturations and retinopathy of extremely prematurity in preterm infants	5/1/11 Presented at PAS 2011 6/8/11 WC: Working on it 9/23/11 WC: Working on it 1/17/12 Drafted. Marie will take over a first author 5/8/12 MG: Revising 7/11/12 MG: Revising 3/8/13 MG: Have made substantial revisions and rerun the analysis on oximeter data using an improved smoothing method (although results did not change). I am close to sending it back to Wally for his review (that should happen in the next couple of weeks). 7/11/13 Sent to coauthors
2. Drafted	Hintz SR; Wraga LA; Barnes PD; Bulas D; Slovis T; Das A; Finer NN; Higgins RD; for the SUPPORT Subcommittee	Brain MRI and cranial US to predict 18-23 month neurodevelopmental outcomes in extremely preterm infants in the SUPPORT NEURO cohort	5/1/12 Presented at PAS 2012 7/6/12 SH: Being written 7/5/13 SH: Estimated draft ready in September 9/11/13 Draft sent to coauthors
2. Drafted	Navarrete CT; Duara S; on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network	Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth	5/1/12 Presented at PAS 2012 7/6/12 CTN: Waiting on some additional analyses before I can complete the first draft of the manuscript. 3/8/13 SWA requested update 7/5/13 SWA requested update 7/11/13 Draft sent to RTI 7/12/13 Draft sent to SubC
3. Reviewing	Ambalavanan N; Carlo WA; Wraga LA; Das A; Laughon MM; Cotten CM; Kennedy KA; Laptook AR; Shankaran S; Walsh MC; Higgins RD	Association of PaCO <sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)	6/2/11 NA: Abstract not accepted at PAS. Manuscript in preparation 1/18/12 NA: Manuscript in preparation – will need additional analyses. 5/7/12 NA: Manuscript in preparation. 7/3/12 NA: Manuscript in preparation. 12/27/12 NA: Manuscript in preparation. 2/21/13 Draft sent to coauthors 7/5/13: Additional analysis done by RTI May 2013; Fourth draft sent to co-authors on 7/5/13 8/5/13 Sent to SUPPORT SubC for review 9/23/13: NA: Two reviews received from Publication Subcommittee; additional reviews awaited and manuscript being revised.
4. Submitted	Kennedy KA; Wraga LA; Higgins RD; Finer NN; Carlo WA; Walsh MC; Laptook AR; Faix RG; Yoder B; Schibler KR; Gantz MG; Das A; Newman NS; Rich W; Phelps DL	Evaluating Retinopathy of Prematurity Screening Guidelines for 24-27 Week Gestational Age Infants	5/1/12 Presented at PAS 2012 5/25/12 Draft sent to coauthors 7/30/12 Sent to SUPPORT Subcommittee 12/14/12 Submitted to Pubs 3/8/13 Delayed Pubs reviews; renews sent to author 2/27/13 KK: plan to submit it to Pediatrics 3/19/13 3/19/13 Submitted to Peds 4/25/13 Peds rejected 6/6/13 Submitting to J Perinatology 6/13/13 J Perinatology rejected 7/18/13 Resubmitted to J Perinatology
5. Revising	LeVan J; Brion LP; Wraga LA; for the NICHD Neonatal Research Network	Changes in Therapy and Outcomes Associated with the SUPPORT Trial	11/15/12 Submitted for PAS 2013 2/11/13 PAS Accepted 6/24/13 Submitted to Peds 9/5/13 Peds rejected; will submit to Jpeds
5. Revising	Stevens TP; Finer NN; Carlo WA; Szilagyi PG; Walsh MC; Gantz MG; Laptook AR; Yoder BA; Faix RG; Newman JE; Das A; Do BT; Schibler K; Rich W; Newman NS; Ehrenkranz	Respiratory Outcomes of the Early CPAP and Pulse Oximetry Trial	11/15/12 Submitted for PAS 2013 11/26/12 Manuscript submitted to Pubs 1/8/13 BT did not receive the manuscript in November; resent it 2/11/13 PAS Accepted 4/30/13 Peds rejected, but can resubmit with revisions

	<p>RA; Peralta-Carcelen M; Vohr BR; Wilson-Costello DE; Yolton K; Heyne RJ; Dusick AM; Evans PW; Vaucher YE; Adams-Chapman I; McGowan EC; Bodnar A; Pappas A; Hintz SR; Acarregui MJ; Fuller J; Goldstein RF; Bauer CR; O'Shea TM; Myers GJ; Higgins RD</p>		<p>6/25/13 Revisions sent to coauthors 8/5/13 Peds rejected revisions; will try J Peds</p>
	<p>Lowe JR; Duncan AF; Bann CM; Fuller J; Hintz SR; Das A; Higgins RD; Watterberg KL; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network</p>	<p>Early working memory as a racially and ethnically neutral measure of outcome in extremely preterm children at 18-22 months</p>	<p><a href="http://www.ncbi.nlm.nih.gov/pubmed/23993309">http://www.ncbi.nlm.nih.gov/pubmed/23993309</a> 5/1/12 Presented at PAS 2012 7/9/12 JL: The manuscript is in preparation and we hope to submit in August. The first draft has been sent to the co-authors. 9/12/12 New version sent to coauthors for review 9/27/12 JL: waiting on Carla Bann to edit the comments specific to statistics. 10/9/12 Submitted to Pubs 11/27/12 Submitted to J Peds 3/8/13 JL: J Peds rejected: revising for resubmission 4/22/13 Submitted to JAMA Pediatrics 5/17/13 JAMA Peds rejected: submitted to Early Human Dev 8/7/13 Early Human Dev accepted 8/17/13 JL submitted to NIHMS</p>
	<p>Vaucher YE; Peralta-Carcelen M; Finer NN; Carlo WA; Walsh MC; Gantz MG; Lupton AR; Yoder BA; Faix RG; Das A; Schibler K; Rich W; Newman NS; Wilson-Costello DE; Vohr BR; McGowan EC; Adams-Chapman I; Heyne RJ; Evans PW; Myers GJ; Poindexter BB; Goldstein RF; Hintz SR; Bauer CR; Yolton K; Pappas A; Dillard RG; Bodnar A; Acarregui MJ; Ehrenkranz RA; Fuller J; Higgins RD</p>	<p>Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial</p>	<p>9/27/11 Draft sent to coauthors 11/15/11 Submitted for PAS 2012 2/7/12 PAS accepted 2/8/12 Submitted to NEJM 3/26/12 NEJM asked to combine the two SUPPORT FU papers into one 5/29/12 Revised combined paper sent to coauthors 7/6/12 YV: Combined paper being submitted to NEJM next week 7/12/12 Combined paper submitted to NEJM 8/13/12 NEJM editing combined paper 9/21/12 NEJM accepted 12/27/12 NEJM published 3/8/13 No PMCID yet 6/27/13 No PMCID yet 9/23/13 No PMCID yet</p>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 11:26 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper clearance

Yes

What has gone through recently??

Breathing outcomes and LeVan papers? Please send the drafts to Carol Blaisdell and copy me

Rose

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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 27, 2013 11:25 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT paper clearance

Should these also go to NHLBI as an FYI?

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Wednesday, September 25, 2013 10:08 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** New paper from SUPPORT trial  
**Attachments:** ambal, association of paco2 with outcomes in support, 2013-08-30.docx

Alan – have spoken with Rose – the NRN and the investigators in the SUPPORT trial have a series of articles/presentations coming up based on additional analyses of data from the study. These articles will come through the clearance system through the OSPAC Director level. I am planning to forward these to you FYI.

The attached paper is the *“Association of PaCO<sub>2</sub> with Outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)”*. It has been submitted to Pediatrics, with the thought that that it will take 3-6 months for review and clearance there.

As you can see from the conclusion, the paper *“demonstrates that maximum PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, maximum PaCO<sub>2</sub> may be useful for risk stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.”*

Cathy has cleared this and with no practice recommendations I’ve cleared it with no need for a disclaimer. While this is FYI, always welcome any comments or thoughts.

Thanks, Mona

*Mona*

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Title:

**Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

**Authors:**

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**Short Title: PaCO<sub>2</sub> and IVH**

**Abbreviations:** BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

**Keywords:** Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

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RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

**Conflicts of interest:** The authors have no conflicts of interest relevant to this article to disclose.

**Word count:** abstract: 250; text of manuscript: 2990 (Introduction, Methods, Results, and Discussion).

**What's known on this subject:** Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

**What this study adds:** Higher  $\text{PaCO}_2$  and greater fluctuation in  $\text{PaCO}_2$  were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of  $\text{PaCO}_2$  with  $\text{FiO}_2$  and days of ventilation support higher maximum  $\text{PaCO}_2$  as a marker of illness severity in extremely premature infants

**ABSTRACT:**

**Objective:** To determine the association of PaCO<sub>2</sub> with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO<sub>2</sub> targets of 85-89% vs 91-95%) and ventilation strategies. Five PaCO<sub>2</sub> variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO<sub>2</sub>], hypocapnic [lowest quartile of Min PaCO<sub>2</sub>], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO<sub>2</sub>]). Adjusted and unadjusted analyses compared PaCO<sub>2</sub> variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all p <0.0001). A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> (r<sub>s</sub>0.55, p<0.0001) & ventilator days (r<sub>s</sub>0.61, p<0.0001). **Conclusions:** Higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). Correlation of PaCO<sub>2</sub> with FiO<sub>2</sub> and ventilator days supports higher Max PaCO<sub>2</sub> as a marker of illness severity.

(Abstract Word Count = 250)

## MANUSCRIPT TEXT

### INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)<sup>1</sup>, periventricular leukomalacia (PVL)<sup>2, 3</sup>, bronchopulmonary dysplasia (BPD)<sup>4</sup>, and neurodevelopmental impairment (NDI)<sup>5</sup>. We have previously shown that both high and low  $\text{PaCO}_2$  levels and wide fluctuations in  $\text{PaCO}_2$  are associated with severe IVH (sIVH; IVH Grades III or IV).<sup>1</sup> Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.<sup>2, 3, 6</sup>

Increased  $\text{PaCO}_2$  increases cerebral blood flow,<sup>7-9</sup> while decreased  $\text{PaCO}_2$  reduces cerebral blood flow.<sup>10</sup> Cerebral blood flow decreases slightly with increased oxygenation<sup>9</sup> but the interactions between  $\text{PaCO}_2$  and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher  $\text{PaCO}_2$ <sup>4, 11, 12</sup> as well as a lower oxygen saturation ( $\text{SpO}_2$ ) target,<sup>13</sup> permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher  $\text{PaCO}_2$  (permissive hypercapnia) as well as a lower  $\text{PaO}_2$  (targeting a lower  $\text{SpO}_2$  range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation and compared outcomes in infants randomly assigned to  $\text{SpO}_2$  targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a  $\text{PaCO}_2 > 65$  mm Hg permitted intubation, while a  $\text{PaCO}_2 < 65$  mm Hg with a  $\text{pH} > 7.20$  was a mandatory extubation criterion) or intubation and surfactant within 1 hour after birth (a  $\text{PaCO}_2 < 50$  mm Hg with a  $\text{pH} > 7.30$  was a mandatory extubation criterion).<sup>13, 14</sup> Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although

infants in the CPAP (higher PaCO<sub>2</sub> target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by postnatal day 7. In the lower SpO<sub>2</sub> target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes although a trend for reduced BPD (physiological definition)<sup>15, 16</sup> was noted in the lower SpO<sub>2</sub> target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).<sup>13</sup> However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups.<sup>17</sup>

It is possible that clinical outcomes that are not significantly different by SpO<sub>2</sub> target groups might be different when the combination of PaCO<sub>2</sub> and SpO<sub>2</sub> (actual or target group) is analyzed. We hypothesized that both extremes of PaCO<sub>2</sub> would be associated with severe IVH, and that effect modification of SpO<sub>2</sub> will be observed, with hypercapnia associated with sIVH in the low but not high SpO<sub>2</sub> group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO<sub>2</sub>, and that higher PaCO<sub>2</sub> will be associated with a higher risk of NDI.

## **PATIENTS AND METHODS**

### **Patient characteristics:**

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.<sup>13, 14</sup> Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical outcomes, and treatment. The characteristics of this population<sup>13</sup> and of the follow-up cohort<sup>17</sup> have been previously reported.

## **PaCO<sub>2</sub> variables**

Five PaCO<sub>2</sub> variables were defined for this observational study, using routine blood gas measurements not governed by study protocol. Data were collected on all PaCO<sub>2</sub> from blood gases done at 3 daily time points closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max PaCO<sub>2</sub>), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO<sub>2</sub> was calculated as described previously:<sup>1</sup> briefly, the sum of all PaCO<sub>2</sub> values multiplied by the corresponding time interval (from previous blood gas) was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5<sup>th</sup>-95<sup>th</sup> centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO<sub>2</sub> over days 1-14 into quartiles. Infants with minimum PaCO<sub>2</sub> in the lowest quartile who were not also in the highest quartile of maximum PaCO<sub>2</sub> were categorized as 'hypocapnic'. Infants with maximum PaCO<sub>2</sub> in the highest quartile who were not also in the lowest quartile of minimum PaCO<sub>2</sub> were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO<sub>2</sub> and the highest quartile of maximum PaCO<sub>2</sub> were categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO<sub>2</sub> level were in quartiles 2-4 and maximum PaCO<sub>2</sub> in quartiles 1-3 were categorized as 'normocapnic'.

## **Other variables**

Maternal hypertension was defined as pregnancy induced hypertension (PIH). Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth.

Prenatal steroids were defined as any use of antenatal steroids. Maximum  $\text{FiO}_2$  was defined as the maximum of  $\text{FiO}_2$  at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as  $\text{FiO}_2 > 0.4$  and mechanical ventilation for 8+ hours in the 1<sup>st</sup> 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),<sup>18</sup> and BPD was defined using the physiologic definition at 36 w PMA.<sup>15, 16</sup> Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.<sup>17</sup>

### Statistical Analysis

The  $\text{PaCO}_2$  and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the  $\text{PaCO}_2$  and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ( $p < .05$ ) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis-generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the maximum  $\text{PaCO}_2$ , the 4 level  $\text{PaCO}_2$  categorical variable, as well as time-weighted  $\text{PaCO}_2$  were obtained using generalized estimating equation (GEE) models for binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same treatment arm in SUPPORT. Variables included in models along with the  $\text{PaCO}_2$  variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes,

and center. SUPPORT treatment group variables (High/Low SpO<sub>2</sub>; CPAP/ventilator) were also included in models that contained maximum PaCO<sub>2</sub> and the 4 level PaCO<sub>2</sub> variable. Interactions of these PaCO<sub>2</sub> and treatment group variables were also included to assess if the effect of PaCO<sub>2</sub> varied by SUPPORT treatment group. A variable for actual median SpO<sub>2</sub> in the first 14 days was included in the model that contained time-weighted PaCO<sub>2</sub>. The interaction of these two variables was included to assess if the effect of time-weighted PaCO<sub>2</sub> varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

## RESULTS

Adjusted analysis for Severe IVH/Death (**Table 1**):

Maximum PaCO<sub>2</sub> was significantly associated with higher odds of sIVH/death (OR 1.39 [95% CI 1.27-1.53] for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ). No interaction was found between PaCO<sub>2</sub> category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (Higher or Lower SpO<sub>2</sub>), but the interaction term for time-weighted PaCO<sub>2</sub> and median SpO<sub>2</sub> in the first 14 days was significant ( $p < 0.05$ ), with a higher OR for PaCO<sub>2</sub> associated with a lower median SpO<sub>2</sub> (OR of 1.6 [1.17-2.17] for median SpO<sub>2</sub> of 91, 1.44 [1.09-1.91] for SpO<sub>2</sub> of 92, 1.30 [0.98-1.73] for SpO<sub>2</sub> of 93, 1.18 [0.85-1.62] for SpO<sub>2</sub> of 94) indicating that a higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

Other variables associated ( $p < 0.05$ ) with sIVH/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

**Adjusted analysis for BPD/Death (Table 2):**

Maximum PaCO<sub>2</sub> (OR 1.57 [1.41-1.75] for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 2.41 [1.89-3.09] for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of BPD/death. The interaction term between PaCO<sub>2</sub> category and treatment group (Higher or Lower SpO<sub>2</sub>) was significant for fluctuators ( $p=0.006$ ), with the OR for fluctuators in the Higher SpO<sub>2</sub> group being 7.4 [2.6-21], as compared to 1.18 [0.51-2.70] for the low SpO<sub>2</sub> group.

Other variables associated ( $p<0.05$ ) with BPD/death included: lower birth weight, male gender, and center.

**Adjusted analysis for NDI/Death (Table 3):**

Maximum PaCO<sub>2</sub> (OR 1.38 [1.25-1.52] for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p<0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 1.44 [1.09-1.90] for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of NDI/death. No significant interactions were noted between PaCO<sub>2</sub> category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (reference group) or hypocapnic infants. Other variables associated ( $p<0.05$ ) with NDI/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

**Adjusted analysis for Death before discharge (Table 4):**

Maximum PaCO<sub>2</sub> (OR 1.36 [1.22-1.51] for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p<0.0001$ ) was associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (reference group) or hypocapnic infants. Other variables associated ( $p<0.05$ ) with death before discharge included: lower birth weight, male gender, absence of PIH, and center.

As higher maximum PaCO<sub>2</sub> may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum FiO<sub>2</sub>, days of mechanical ventilation, and severe illness), correlations of maximum PaCO<sub>2</sub> with maximum FiO<sub>2</sub>, days of ventilation, and severe illness (as previously defined) were calculated. Maximum PaCO<sub>2</sub> was positively correlated with both maximum FiO<sub>2</sub> (Spearman correlation coefficient = 0.55, p<0.0001) and days of ventilation (Spearman correlation coefficient = 0.61, p<0.0001). There was also a significant difference in PaCO<sub>2</sub> level by infants defined as having severe illness (median maximum PaCO<sub>2</sub>=78) vs. infants having no severe illness (median maximum PaCO<sub>2</sub>=61), p <0.0001.

**Unadjusted Results (Supplemental Tables 1-4):**

All PaCO<sub>2</sub> variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in PaCO<sub>2</sub> as compared to those without sIVH. Maximum PaCO<sub>2</sub> demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum PaCO<sub>2</sub> between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted PaCO<sub>2</sub> were statistically highly significant (p<0.0001) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted PaCO<sub>2</sub> compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

## DISCUSSION

We found that extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO<sub>2</sub> in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO<sub>2</sub>, days of ventilation, and severe illness). A higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the higher SpO<sub>2</sub> target group and not in the lower SpO<sub>2</sub> target group.

Our study has the limitation that infants in the SUPPORT trial<sup>13, 14</sup> were not primarily randomized to different PaCO<sub>2</sub> ranges as in the randomized trials of permissive hypercapnia<sup>4, 12, 19</sup> but to interventions (Early CPAP vs. intubation/surfactant) with different PaCO<sub>2</sub> goals. Data on corresponding ventilator settings and oxygenation index are not available to determine if reduction of PaCO<sub>2</sub> using higher ventilator settings was associated with better outcome. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, specific criteria for intubation and extubation were used, and trained research coordinators collected data. Eighteen to 22 month follow-up was achieved in almost 94% of infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups, probably because randomization in this trial most likely led to a similar range of PaCO<sub>2</sub> in both SpO<sub>2</sub> groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in PaCO<sub>2</sub> secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.<sup>14</sup> An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (higher or lower SpO<sub>2</sub> target), in order to distinguish illness severity and effects of

treatment group allocation (e.g. higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO<sub>2</sub> levels and wide fluctuations in PaCO<sub>2</sub> are associated with an increased risk of sIVH.<sup>1</sup> The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO<sub>2</sub> were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO<sub>2</sub>. As maximum PaCO<sub>2</sub> was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO<sub>2</sub> had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average PaCO<sub>2</sub> in combination with a lower SpO<sub>2</sub> being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) PaCO<sub>2</sub> even in infants without severe IVH was  $\geq 48$  mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the “permissive hypercapnia” range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.<sup>12</sup> Our data indicate clinical practices in academic centers have evolved to maintain PaCO<sub>2</sub> in the permissive hypercapnia range. However, as the maximum PaCO<sub>2</sub> exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO<sub>2</sub> within this narrow range is difficult.

A higher maximum and time-weighted PaCO<sub>2</sub> and a greater magnitude of fluctuation in PaCO<sub>2</sub> were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher

PaCO<sub>2</sub> rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO<sub>2</sub> elimination for a given minute ventilation, due to a higher alveolar CO<sub>2</sub> (P<sub>A</sub>CO<sub>2</sub>). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing PaCO<sub>2</sub>, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.<sup>4, 11, 12, 19</sup> An interesting finding in the present study was that greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the higher SpO<sub>2</sub> but not in the low SpO<sub>2</sub> group. It is speculated that higher oxygen exposure in the higher SpO<sub>2</sub> group may interact with volutrauma/atelectrauma associated with fluctuating PaCO<sub>2</sub> possibly increasing the risk for BPD/death.

Maximum PaCO<sub>2</sub> was also significantly associated with higher NDI/death, confirming our previous single-center study.<sup>5</sup> This association may be secondary to maximum PaCO<sub>2</sub> being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.<sup>20</sup> Alterations in PaCO<sub>2</sub> may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO<sub>2</sub><sup>7-9</sup> may result in sIVH<sup>1</sup> and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO<sub>2</sub><sup>10</sup> may lower white matter perfusion and result in periventricular leukomalacia (PVL).<sup>2, 3, 6</sup> Brain injury associated with extremes of PaCO<sub>2</sub> may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.<sup>21, 22</sup>

In conclusion, our work demonstrates that maximum PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, maximum PaCO<sub>2</sub> may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.

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**Table 1:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of severe IVH/death

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.39 (1.27-1.53)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.11 (0.73-1.67)	0.63
<b>Hypercapnic</b>	2.60 (1.77-3.82)	<0.0001
<b>Fluctuator</b>	2.81 (1.68-4.72)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub>** (per 10 mm Hg)</b>		
<b>Median SpO<sub>2</sub>=91</b>	1.60 (1.17-2.17)	0.003
<b>Median SpO<sub>2</sub>=94</b>	1.18 (0.85-1.62)	0.32

\*\* interaction term for time-weighted PaCO<sub>2</sub> x Median SpO<sub>2</sub> in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted PaCO<sub>2</sub> depended on level of Median SpO<sub>2</sub>.

**Table 2:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of BPD/death

PaCO <sub>2</sub> Variable	Adjusted Odds Ratio (95% CI)	p-value
Max PaCO <sub>2</sub> (per 10 mm Hg)	1.57 (1.41-1.75)	<0.0001
<b>PaCO<sub>2</sub> Category: <u>Higher SpO<sub>2</sub></u></b>		
Hypocapnic	0.73 (0.46-1.16)	0.18
Hypercapnic	2.54 (1.41-4.60)	0.002
Fluctuator	7.4 (2.6-21.0)	0.0002
Normocapnic	REFERENCE	-
<b><u>Lower SpO<sub>2</sub></u></b>		
Hypocapnic	1.01 (0.63-1.63)	0.96
Hypercapnic	3.38 (1.93-5.93)	<0.0001
Fluctuator	1.18 (0.51-2.70)	0.70
Normocapnic	REFERENCE	-
Time weighted PaCO <sub>2</sub> (per 10 mm Hg)	2.41 (1.89-3.09)	<0.0001

\*\* interaction term for PaCO<sub>2</sub> category x treatment group (Higher or Lower SpO<sub>2</sub>) was significant for Fluctuators

**Table 3: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of NDI/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.38 (1.25-1.52)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.03 (0.69-1.53)	0.90
<b>Hypercapnic</b>	2.69 (1.82-3.96)	<0.0001
<b>Fluctuator</b>	3.07 (1.84-5.12)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.44 (1.09-1.90)	0.009

**Table 4:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of death before discharge

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.36 (1.22-1.51)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	0.90 (0.54-1.50)	0.07
<b>Hypercapnic</b>	2.47 (1.61-3.77)	<0.0001
<b>Fluctuator</b>	1.88 (1.03-3.43)	0.04
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.28 (0.94-1.74)	0.12

**Supplemental Tables**

**Supplemental Tables:**

**Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH**

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>	
PaCO <sub>2</sub> , level	minimum	#	163	1098		325	971	
		Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
		Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
PaCO <sub>2</sub> , level	maximum	#	163	1098		325	971	
		Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
		Median, IQR	75 (63-85)	65.5 (55-75)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , deviation	standard	#	163	1077		314	951	
		Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
		Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , weighted	time-	#	163	1098		325	971	
		Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
		Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
PaCO <sub>2</sub> category:	#	163	1098		325	971		

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
	# (%)			<0.0001			<0.0001
Hypocapnic		30 (18.4)	205 (18.7)		48 (14.8)	189 (19.5)	
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65(39.9)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO <sub>2</sub> group, Higher or Lower O <sub>2</sub>	#	164	1106		335	979	
	High O <sub>2</sub> , # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO <sub>2</sub> DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race:	# (%)						
NH Black		55 (33.5)	421 (38.1)	0.016	112 (33.4)	376 (38.4)	0.09
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic			BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
PaCO <sub>2</sub> , level	minimum	#	441	659		639	659	
		Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
		Median, IQR	33 (29-37)	34 (30-38)	0.015	33 (29-38)	34 (30-38)	0.25
PaCO <sub>2</sub> , level	maximum	#	441	659		639	659	
		Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
		Median, IQR	72 (64-83)	60 (50-69)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
PaCO <sub>2</sub> , deviation	standard	#	438	642		625	642	
		Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
		Median, IQR	9.8 (7.8- 11.8)	8.0(5.7-9.9)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
PaCO <sub>2</sub> , weighted	time-	#	441	659		639	659	
		Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
		Median, IQR	51 (47.3- 54.3)	46.2 (41.1- 50.4)	<0.0001	51.2 (47.2- 55.2)	46.2 (41.1- 50.4)	<0.0001
PaCO <sub>2</sub> category:	#	441	659		639	659		
Hypocapnic	# (%)	78 (17.7)	138 (20.9)	<0.0001	100 (15.7)	138 (20.9)	<0.0001	
Hypercapnic		101 (22.9)	59 (9.0)		170 (26.6)	59 (9)		
Fluctuator		48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)		
Normocapnic		214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)		
Treatment: CPAP or Surfactant group	#	442	666		650	666		
	CPAP, (%)	# 223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25	

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, Higher or Lower O <sub>2</sub>	#	442	666		650	666	
	High O <sub>2</sub> , # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO <sub>2</sub> DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	0.013	221 (34)	268 (40.2)	0.02
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	0.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	0.004	193 (29.7)	240 (36.0)	0.01

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
PaCO <sub>2</sub> , level	minimum #	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	0.001	33 (28-38)	33 (30-38)	0.95
PaCO <sub>2</sub> , level	maximum #	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<0.0001	76 (66-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , standard deviation	standard #	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , time- weighted	time-#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)	<0.0001
PaCO <sub>2</sub> category:	#	98	872		346	872	
Hypocapnic	# (%)	22 (22.5)	171 (19.6)	<0.0001	51 (14.7)	171 (19.6)	<0.0001
Hypercapnic		25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)		135 (39.0)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, Higher or Lower O <sub>2</sub>	#	98	878		356	878	
	High O <sub>2</sub> , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO <sub>2</sub> DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<0.0001	734 (621-870)	850 (710-995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race:	# (%)						
NH Black		37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
NH White		37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other		3 (3.1)	30 (3.4)		14 (3.9)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
PaCO <sub>2</sub> , maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
PaCO <sub>2</sub> category:	#	227	991	
Hypocapnic	# (%)	26 (11.5)	196 (19.8)	<0.0001
Hypercapnic		82 (36.1)	140 (14.1)	
Fluctuator		29 (12.8)	64 (6.5)	
Normocapnic		90 (39.7)	591 (59.6)	
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO <sub>2</sub> group, Higher or Lower O <sub>2</sub>	#	237	997	
	High O <sub>2</sub> , # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO <sub>2</sub> DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race:	# (%)			
NH Black		77(32.5)	381 (38.2)	0.26
NH White		96 (40.5)	397 (39.8)	
Hispanic		53 (22.4)	186 (18.7)	
Other		11 (4.6)	33 (3.3)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	Yes, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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**Subject:** RE: SUPPORT secondary paper for NICHD clearance  
**Date:** Wednesday, September 25, 2013 8:41:44 AM

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For the paper submitted to clearance – usually takes 3-6 months.

For the Neuro imaging paper – this one is still in internal NRN review so will likely come for clearance in the next month.

I will let you know whenever we have SUPPORT publications upcoming

Thanks

Rose

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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#)  
**Sent:** Wednesday, September 25, 2013 8:40 AM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT secondary paper for NICHD clearance

Also—when were you hoping for publication – my other thought is that Alan in turn may wish to tell KH about this – perhaps when accepted

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
Analysis and Communication  
*Eunice Kennedy Shriver* National Institute of  
Child Health and Human Development  
National Institutes of Health, DHHS  
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31 Center Drive  
Bethesda, MD 20892-2425  
Phone: 301.496.1877/Fax: 301.496.0588  
Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Wednesday, September 25, 2013 8:31 AM  
**To:** [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E] ([archerst@mail.nih.gov](mailto:archerst@mail.nih.gov))  
**Subject:** RE: SUPPORT secondary paper for NICHD clearance

Hi Rose in reading this reading this –was thinking that I will forward a copy, FYI, to Alan and cc you, Cathy, and Stephanie and let Alan know that if he has any questions he can ask you but that you are writing to send to it forward – would that work for you?

*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
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Eunice Kennedy Shriver National Institute of  
Child Health and Human Development  
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Email: [rowem@mail.nih.gov](mailto:rowem@mail.nih.gov)

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**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 2:48 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT secondary paper for NICHD clearance

Sure –sorry for any delay- -for some reason it did not show in the queue for my review –although I can find it is in the system –seems like it was put in track 1 not for my review and then Cathy asked that we look at it—so that technicality kept it from showing up in the review queue – will look at now

*Mona*

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 12:17 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** SUPPORT secondary paper for NICHD clearance

Mona  
Stephanie entered a SUPPORT secondary paper into the clearance tracking system titled:  
**Association of PaCO2 with outcomes in SUPPORT.**  
It is ID #14147.

Can you let us know if there are concerns with it? It has been sitting for a few weeks.

Thanks  
Rose  
Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT secondary paper for NICHD clearance  
**Date:** Wednesday, September 25, 2013 8:32:30 AM

---

Sure

This is fine

We have a couple more SUPPORT papers in the works – one looks at neuro imaging and 2 year outcomes (500+ infants with timed neuro studies)– we plan to send to NEJM

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
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*Mona*

Mona Jaffe Rowe, M.C.P.  
Associate Director for Science Policy,  
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*Eunice Kennedy Shriver* National Institute of  
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National Institutes of Health, DHHS  
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**Sent:** Tuesday, September 24, 2013 12:17 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** SUPPORT secondary paper for NICHD clearance

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Thanks  
Rose  
Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Boilerplate | Hintz, SUPPORT Neuro 18-22 Month FU  
**Date:** Tuesday, September 24, 2013 3:59:13 PM  
**Attachments:** [Attach0.html](#)  
[Boilerplate, Hintz, SUPPORT Neuro FU, 2013-09-06.docx](#)

---

Are the FU PI's not going to be authors in the masthead?? I think I must have missed this – how did we do it for Yvonne's paper?

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]  
**Sent:** Tuesday, September 24, 2013 3:52 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fwd: Boilerplate | Hintz, SUPPORT Neuro 18-22 Month FU

I am suprised when I see papers that have limited authorship. Were all F/U PIs given the oppportunity to participate?  
THANKS

Barbara J. Stoll, MD  
George W. Brumley, Jr., Professor and Chair  
Department of Pediatrics, Emory University School of Medicine  
Director, The Pediatric Center of Emory and Children's Healthcare of  
Atlanta

President, Emory-Children's Center  
1760 Haygood Drive  
Atlanta, GA 30322  
Office: 404-727-2456 Fax: 404-727-5737  
[bstoll@emory.edu](mailto:bstoll@emory.edu)

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

Dear PIs,

Attached is an acknowledgements boilerplate for Susan Hintz's paper, "Neonatal neuroimaging and neurodevelopmental outcomes at 18-22 months corrected age in extremely preterm infants: The SUPPORT NEURO Study." A draft of this paper will be sent out when it is ready for Publications review.

As stated on the boilerplate, this paper includes:

- **SUPPORT recruitment 2004-2009**
- **18-22 Month Follow-up around 2006-2011**

Because the paper includes FU, I have listed all of the FU examiners for each site that I am aware of. Please look over the list carefully. Since I don't have start and end dates for most of these people, I had to include all of them, you will likely need to delete some and add others.

As always, please look over the attached boilerplate to make sure that:

- All relevant centers are included
- All relevant personnel are included with full names and degrees

Please send me your responses by **Tuesday, October 8<sup>th</sup>**.

Thank you,

Stephanie

---

Stephanie Wilson Archer

The Eunice Kennedy Shriver

National Institute of Child Health and Human Development

Pregnancy & Perinatology Branch

6100 Executive Boulevard, Room 4B03

Rockville, MD 20852

Tel. 301-496-0430

Fax 301-496-3790

[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

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- All relevant centers are included
- All relevant personnel are included with full names and degrees

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Thank you,

Stephanie

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Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
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Pregnancy & Perinatology Branch  
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Rockville, MD 20852

Tel. 301-496-0430  
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[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

## Neonatal neuroimaging and neurodevelopmental outcomes at 18-22 months corrected age in extremely preterm infants: The SUPPORT NEURO Study

Susan R. Hintz, MD MS Epi<sup>1</sup>; Patrick D. Barnes, MD<sup>1</sup>; Dorothy Bulas, MD<sup>2</sup>; Thomas L. Slovis, MD<sup>3</sup>; Neil N. Finer, MD<sup>4</sup>; Lisa A. Wrage, MPH<sup>5</sup>; Abhik Das, PhD<sup>6</sup>; Jon E. Tyson, MD MPH<sup>7</sup>; David K. Stevenson, MD<sup>1</sup>; Waldemar A. Carlo, MD<sup>8</sup>; Michele C. Walsh, MD MS<sup>9</sup>; Abbot R. Lupton, MD<sup>10</sup>; Bradley A. Yoder, MD<sup>11</sup>; Krisa [REDACTED] Van Meurs, MD<sup>1</sup>; Roger G. Faix, MD<sup>12</sup>; Wade Rich, RRT<sup>1</sup>; Nancy S. Newman, RN<sup>1</sup>; Helen Cheng, MS<sup>5</sup>; Rosemary D. Higgins, MD<sup>12</sup>, for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

### Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial Neuroimaging Secondary Protocol through cooperative agreements. While NICHD staff had input into the study design, conduct, analysis, and manuscript drafting, the comments and views of the authors do not necessarily represent the views of the NICHD.

Comment [swa1]:  
Recruitment: 2004-2009  
FU: 2006-2011

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator), Marie Gantz, Lisa Wrage, and Helen Cheng (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

<sup>1</sup> Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA

<sup>2</sup> [REDACTED]

<sup>4</sup> University of California at San Diego, San Diego, CA

<sup>5</sup> Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

<sup>6</sup> Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD

<sup>7</sup> Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX

<sup>8</sup> Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

<sup>9</sup> Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH

<sup>10</sup> Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI

<sup>11</sup> Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT

<sup>12</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

[REDACTED] and Women & Infants Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Betty R. Vohr, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksniris, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN; Dan Gingras, RRT; Regina A. Gargus, MD FAAP; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MD CAES; Martha R. Leonard, BA BS; Sarah Lillie, RRT; Kalida Mehta; James R. Moore, MD; Lucy Noel; Suzy Ventura; Rachel V. Walden; Victoria E. Watson, MS CAS.

[REDACTED] Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Deanne E. Wilson-Costello, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN; Arlene Zadell, RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

[REDACTED] School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Ricki F. Goldstein, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

[REDACTED] Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

[REDACTED] University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; Anna M. Dusick, MD FAAP; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

[REDACTED] (U10 HD36790) – Abhik Das, PhD; Marie G. Gantz, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; W.

Kenneth Poole, PhD; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

[REDACTED] and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hall E. Weiss, MD.

[REDACTED], Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Elisabeth C. McGowan, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nysten, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

[REDACTED] at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Myriam Peralta-Carcelen, MD MPH; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

[REDACTED] Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Neil N. Finer, MD; Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Yvonne E. Vaucher, MD MPH; Wade Rich, RRT; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Cheryl Runyan; James Wilkes; Paul Zlotnik.

[REDACTED] Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Michael J. Acarregui, MD; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

[REDACTED], Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowitz, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroeger, BA.

[REDACTED] Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janel Fuller, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

[REDACTED] Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augustino; Julie Babish Johnson, MSW;

Erica Bunnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

██████████ Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

██████████ Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

██████████ Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Bradley A. Yoder, MD; Roger G. Faix, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

██████████ Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Diliard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Alfred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

██████████ Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** (kzaterka@rti.org)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: clinicaltrials.gov  
**Date:** Tuesday, September 24, 2013 12:49:30 PM

---

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Hirschfeld, Steven (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 12:49 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: clinicaltrials.gov

Will get back to you on all three. I anticipate that all will be resolved before the end of the this week but will confirm.

Kind regards,

Steven H.

Steven Hirschfeld, MD PhD  
Captain, U.S. Public Health Service  
Associate Director for Clinical Research  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Director  
National Children's Study  
Chief Medical Officer  
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425  
Bethesda, MD 20914 (for express packages use 20892)

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, September 24, 2013 12:46 PM  
**To:** Hirschfeld, Steven (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: clinicaltrials.gov

Steven

RTI entered two trials into clinicaltrials.gov that have not yet been posted. One is a large phase 3

inositol for retinopathy study and the second is a term and late preterm hypotension study. DO you know when we will get NCT numbers? We need them to go to the IRBs.

Also when will the SUPORT data be posted?

Thanks for your help

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Hirschfeld, Steven (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 4:38 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: clinicaltrials.gov

See below.

Steven Hirschfeld, MD PhD  
Captain, U.S. Public Health Service  
Associate Director for Clinical Research  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Director  
National Children's Study  
Chief Medical Officer  
U.S. Public Health Service Rapid Deployment Force PHS-1

31 Center Drive, MSC-2425  
Bethesda, MD 20914 (for express packages use 20892)

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:07 PM  
**To:** Hirschfeld, Steven (NIH/NICHD) [E]  
**Subject:** clinicaltrials.gov

Steven –

Were you able to get the SUPPORT results posted on clinicaltrials.gov?

--Still pendind.

Do you need anything else from the data coordinating center?

--No, so far so good.

Also, once the records are totally switched to RTI, the NRN would like to list the sponsor as "NICHD Neonatal Research Network." There are a few other neonatal research networks around the world and we would like to avoid confusion. Let me know if this is appropriate.

--Seems perfect. Please proceed.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Namasivayam Ambalavanan](#)  
**To:** "Mcbrien, James, D"  
**Cc:** [Truog, William \(MD\)](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) \*Sent on Behalf of William E. Truog, MD\*  
**Date:** Friday, September 20, 2013 4:52:15 PM

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Thank you!  
Ambal

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**From:** [Mcbrien, James, D \[mailto:jdmcbrien@cmh.edu\]](mailto:jdmcbrien@cmh.edu)  
**Sent:** Friday, September 20, 2013 3:38 PM  
**To:** [Namasivayam Ambalavanan](#)  
**Cc:** [Truog, William \(MD\)](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) \*Sent on Behalf of William E. Truog, MD\*

Good afternoon Dr. Ambalavanan,

Please find attached two de-identified reviews of the manuscript entitled "Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)". If additional reviews are received, they will be forwarded to you as soon as possible.

Thanks,

Jim

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Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at [informationsecurityofficer@cmh.edu](mailto:informationsecurityofficer@cmh.edu) and expunge this communication without making any copies. Thank you for your cooperation.

**From:** McGowan, Elisabeth C  
**To:** Das, Abhik; Kristi Watterberg; Satvan Lakshminrusimha; kurt.schibler@cchmc.org; Bill Trugg; RAP32@columbia.edu; mcw3@cwru.edu; hooindex@iu.edu; vanmeurs@leland.stanford.edu; Higgins, Rosemary (NIH/NICHD) [F]; goldb008@mc.duke.edu; sshankar@med.wayne.edu; Uday Devaskar; Leif Nelin; [SCRN] Stoll, Barbara; M.D. Wally Carlo; Wallace, Dennis; Gantz, Marie; Edward Bell; Anne Marie Reynolds; Barbara Schmidt; Carl D'Angio; Kathleen.A.Kennedy@uth.tmc.edu; Pablo.Sanchez@UTSouthwestern.edu; alaotook@WIHL.org  
**Cc:** Ivan.Frantz@childrens.harvard.edu; Roger.Faix@hsc.utah.edu; SDuara@med.miami.edu; Neil.Finer; moshea@wfubmc.edu; richard.ehrenkranz@vale.edu; Davis, Jonathan  
**Subject:** Submitted to OHRP  
**Date:** Wednesday, September 18, 2013 3:25:54 PM  
**Attachments:** Guidelines for Standard of Care Research.doc

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Also for your information. The attached was submitted to OHRP by Jonathan Davis after the meeting and is being passed along to the group.

Liz

Elisabeth C. McGowan, MD  
Tufts Floating Hospital for Children  
Director NICU Follow Up

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Tufts Medical Center HIPAA Hotline at (617) 636-4422. If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.

## **Establishing Guidelines for Standard of Care Research**

### **Department of Health and Human Services Meeting, August 28, 2013**

I applaud DHHS for conducting the meeting in Washington to develop guidance regarding standard of care and comparative effectiveness research. There is a clear need for this guidance since this type of research is increasing in frequency and importance. However, after attending the meeting, I was struck by the many inaccuracies and inconsistencies reflected in many of the comments and strongly believed it was crucial to “set the record straight”, so the committee would better understand the context of the SUPPORT study. I am a Professor of Pediatrics at Tufts University School of Medicine and my entire research career has involved studying the harmful effects of oxygen and mechanical ventilation on the lungs of preterm infants. I have authored approximately 50 manuscripts and book chapters and lectured extensively nationally and internationally on this subject. The preterm infant population has been largely ignored over the past 20 years and outcomes have not substantially improved during this time. ClinicalTrials.gov has 55,000 clinical trials registered, with <300 dealing with preterm infants, so many more studies are needed to develop better clinical approaches to improve outcome (Davis JM et al, JAMA, October 2012).

The SUPPORT study was conceived in the late 1990's for several reasons. Approximately 60% of all extremely low birth weight (ELBW) preterm infants who survived were developing bronchopulmonary dysplasia (BPD), a chronic form of lung injury caused by exposure to oxygen (even room air is supraphysiologic) and positive pressure mechanical ventilation (despite surfactant administration). BPD was associated with repeated pulmonary infections and asthma when infants got older. Although it was accepted that early intubation, surfactant administration and mechanical ventilation improved survival, Columbia University in NY had published that their incidence of BPD were less than half of most other centers with comparable survival rates. This center used early nasal continuous positive airway pressure (CPAP) exclusively and rarely intubated infants and gave surfactant, which they believed caused less lung injury and BPD. In an attempt to better define best practices (there was tremendous debate on the optimal ventilatory strategies), the SUPPORT trial randomized infants to early CPAP vs. intubation and surfactant administration.

Next, we absolutely did not know the optimal oxygen saturation ranges for preterm infants (oxygen saturation monitoring only started routinely in preterm infants in the late 1980's). Many studies quoted by speakers concerning low or high oxygen levels occurred in the era prior to routine oxygen saturation monitoring and are not pertinent or relevant. The Fetus and Newborn Committee of the AAP reviewed all available oxygen saturation data (from several small studies) and concluded that a range of 85-95% would be safe and minimize complications (e.g. BPD and Retinopathy of Prematurity). In addition, neonatal investigators throughout the world felt that this was one of the most important factors we needed to study and SUPPORT as well as the trials from Canada and Australia were designed. The following misconceptions need clarification:

- 1. The AAP would not have recommended this oxygen saturation range if there were any “concerns” it was dangerous. In addition, all three studies involving multiple investigators in multiple countries were designed using similar target ranges and approaches (masked oximeters) and this would not have occurred if there was any existing evidence that this was dangerous.**
- 2. A major criticism is randomizing infants to a higher or lower range would eliminate the central range which would be safer and associated with fewer complications. This is not true – most centers maintained infants in the lower range for clinical**

**purposes. This reduced the incidence of ROP and was not thought to be associated with excess mortality. This practice only changed after the results of SUPPORT were known. Also, taking away the treating physician's judgment on appropriate oxygen levels was felt to be particularly egregious. However, the protocol clearly stated that if in the Attending Physician that an infant needed to be removed from the study for medical indications, this could be done.**

- 3. The consent form for SUPPORT was designed approximately 13 years ago. Informed Consent forms have evolved significantly over that time. The other two oxygen studies and Consent Forms were designed years after SUPPORT. While the consent form could have been better, it is not reasonable to judge a 2000 process using 2013 standards.**
- 4. It is critically important to understand that based on all available information, death was not a "reasonably foreseeable risk" for the study and did not need to be disclosed. The consent form from the Canadian study did not mention death and this study did not find a difference in mortality between the high and low ranges.**
- 5. It was mentioned that since death was listed in the protocol, it indicates that the investigators were aware that this might be increased by participating in the study. This is incorrect – if you are examining eye or lung disease in preterm infants, an infant must survive in order to develop these complications. With mortality in this population approximately 20-25%, we routinely use a combined endpoint of being alive and without the complication as the primary outcome variable of a study. We had hoped that SUPPORT would demonstrate that the lower range would result in more infants being alive and without developing BPD or ROP. *No investigator in the entire world honestly believed that death would increase in the lower target range.***
- 6. The development of ROP does not mean the infant will become blind. Most ROP regresses on its own, never needs treatment, and does not lead to blindness. In fact, the follow-up SUPPORT study showed no difference in blindness between the two experimental groups (while the incidence of ROP was higher in the higher target range as expected, this did not translate into more blindness). In addition, the SUPPORT follow-up study also failed to find any difference in the risk of serious brain injury (e.g. cerebral palsy) between the groups.**
- 7. Despite decades of clinical care and clinical research, the optimal time to extubate an infant and place them on CPAP is not known. The protocol attempted to better define optimal extubation criteria and this did not "force" infants to be removed**

**from the respirator. At the present time, 50% of accidental extubations that occur in the NICU end up with the infant remaining off the ventilator. Once again, if an infant needed to be on one ventilator approach or the other based on the opinion of the Attending Neonatologist, the protocol allowed for the infant to exit the study and have individualized treatment continued or instituted.**

- 8. We are constantly trying to establish best practices in neonatal intensive care and develop protocols and standardize care which has definitively been shown to improve outcome. A number of comments called for an additional control group for all CER studies which would allow individual variation among the multiple physicians who care for study patients. This would add a third arm to every study and increase the time, number of patients, complexity, and costs of these types of trials. In the SUPPORT trial, infants whose parents were approached for consent and refused were still followed and their data recorded. Although not randomized, these infants had a higher mortality rate than either of the groups studied in SUPPORT. This approach could be adopted for other CER studies in order to simplify the suggested approach.**
  
- 9. From reading the OHRP action letter and from hearing comments at the meeting, it did not appear that OHRP consulted with qualified Neonatologists with expertise in clinical care, study design, and research ethics prior to taking their action. The FDA has an Office of Pediatric Therapeutics with considerable expertise in this area as does the CTSA Consortium Child Health Oversight Committee at NCATS. In an era of increased transparency and collaboration, HHS agencies should be strongly required to widely consult appropriate experts to make sure all of their facts are correct prior to taking this type of action in the future.**

Jonathan M. Davis, MD

Vice-Chair of Pediatrics for Academic Affairs

Chief of Newborn Medicine

Tufts Medical Center

Professor of Pediatrics

Tufts University School of Medicine

Boston, MA

**September 1, 2013**

**From:** [Namasivayam Ambalavanan](#)  
**To:** [Kennedy, Kathleen A](#); [Shankaran, Seetha](#); [Michael Cotten, M.D.](#); [Namasivayam Ambalavanan](#)  
**Cc:** [Walsh, Michele](#); [Abhik Das](#); [Gantz, Marie](#); [Wally Carlo, M.D.](#); [Abbot Laptook](#); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]; [Matt Laughon](#); [Wrage, Lisa Ann](#); [Archer, Stephanie \(NIH/NICHD\)](#) [E]; [Namasivayam Ambalavanan](#)  
**Subject:** RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement  
**Date:** Wednesday, September 18, 2013 12:50:22 PM

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Hi Kathleen,

Thank you for the insightful comments. Regarding comment #1, we did include data on PaCO2 from every day between days 1 and 14, not just days 1, 3, 7, and 14 (we listed the median # of gases on days 1, 3, 7, and 14 just to indicate that the number of gases each day diminished over time; Also, the max FiO2 was defined only on day 1, 3, 7, and 14). For comment # 4 (most of the email below), I will think over how best to reword the Discussion – the article by Kramer by al has some interesting arguments. I agree that there are issues with the handling of independent variables vs. interactions. I think the main reason for looking at achieved PaCO2 and randomized assignment for SpO2 is because we did not really have an allocation strategy for PaCO2 (the CPAP vs. Intubation groups did not have an a priori separation in PaCO2 defined) and the SpO2 achieved was difficult to define (the offset between what the clinician saw, which drove clinical decisions, and what was the actual SpO2). Agree that looking at associations between categories of achieved PaCO2 and achieved SpO2 for outcomes would be interesting, and the associations would probably be stronger, Will think about it some more,

Thanks,  
Ambal

---

**From:** [Kennedy, Kathleen A \[mailto:Kathleen.A.Kennedy@uth.tmc.edu\]](mailto:Kathleen.A.Kennedy@uth.tmc.edu)  
**Sent:** Wednesday, September 18, 2013 10:30 AM  
**To:** [Namasivayam Ambalavanan](#); [Shankaran, Seetha](#); [Michael Cotten, M.D.](#)  
**Cc:** [Walsh, Michele](#); [Abhik Das](#); [Gantz, Marie](#); [Wally Carlo, M.D.](#); [Abbot Laptook](#); [NIH](#); [Matt Laughon](#); [Wrage, Lisa Ann](#); [Archer, Stephanie \(NIH/NICHD\)](#) [E]; [Namasivayam Ambalavanan](#)  
**Subject:** RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement

Sorry this has taken me a while. I've really been struggling with how to summarize and present this in a way that's informative and adds to what's already been published about this. (I've also been on service, out of town, etc.)

I'm still troubled by how we're handling the independent variables that were randomly allocated vs the ones that were not. The most robust assessments of the effects of different O2 sat ranges and different PaCO2 ranges would come from the primary unadjusted (except for stratification by center) analyses (looking at BPD, death/BPD, ICH, death/ICH as outcomes) according to the strata in the factorial design that should have achieved different distributions in achieved O2 sats and achieved PaCO2. Ideally you would also look at the interaction although the trial wasn't powered for this. I think we should view these analyses as the most unbiased (albeit underpowered) assessments of causal relationships. These analyses aren't much different from the analyses of secondary outcomes in the primary manuscripts for SUPPORT.

Once you turn this into an observational study of different achieved PaCO2 ranges, confounding by illness severity makes a mess of things. It doesn't make obvious logical sense to me that you're

looking at PaCO<sub>2</sub> according to achieved (rather than allocation strategy for) PaCO<sub>2</sub> but you're evaluating the effect of O<sub>2</sub> sats and interaction using the randomized assignment (rather than achieved distributions) for O<sub>2</sub> sat ranges. Why can't you have categories for achieved O<sub>2</sub> sats that are similar to the categories you derived for achieved PaCO<sub>2</sub>?

Then you could do observational analyses of the associations between categories of achieved PaCO<sub>2</sub> and achieved O<sub>2</sub> sat with the outcomes of interest (after adjustment for the assigned allocation). Presumably the associations here would be much stronger than the effects observed by group assignment alone. You could then conclude (similar argument to the one made by Kramer et al in the Pacifier RCT, see attached) that these findings suggest that associations observed in prior observational studies are most likely due to confounding by illness severity rather than causal relationships. I think this line of reasoning would be more provocative and interesting to reviewers and readers.

I've also added a few minor comments in the manuscript. I sent the acknowledgment email to Bill. I guess you might want to try submitting this as is. I realize it would be a lot more work to make changes as above but I think it would be viewed as more provocative and interesting.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Thursday, August 01, 2013 1:52 PM  
**To:** Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wraage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan  
**Subject:** RE: PaCO<sub>2</sub> manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement  
**Importance:** High

Dear All,

Thank you for your comments on the previous drafts. Attached is the fifth draft of our manuscript evaluating PCO<sub>2</sub> in SUPPORT. There are minor changes since the previous draft. The paper has been formatted for PEDIATRICS. The word count is a bit high (3075 rather than 3000), so will need a little trimming. Also attached is the Authorship Agreement – please complete and email (click the button on form to automatically email it to me) or print and fax (205-934-3100) to me. Once I hear back from anyone, if there are no further major comments, I will send to the Publications subcommittee, and then make changes in response to Publication Subcomm Reviewer comments, and then finally send for NICHD Clearance before submission.

Sincerely,  
Ambal

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**From:** Namasivayam Ambalavanan [[NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu)]

**Sent:** Friday, July 05, 2013 11:35 AM  
**To:** Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Shankaran, Seetha; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Fourth draft of July 5, 2013

Dear All,

Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

- 1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
- 2) Some clarifications of methods and explanations in Discussion.
- 3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,  
Ambal

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, March 05, 2013 12:54 PM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis ( Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Thursday, February 21, 2013 10:37 AM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : first draft of Feb21, 2013  
**Importance:** High

Dear All,

Attached is a first draft of a manuscript relating PaCO<sub>2</sub> in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)

Thank you for all your help,

Best regards,

Ambal

Namasivayam Ambalavanan MD

Division of Neonatology,

Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology

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---

**From:** Namasivayam Ambalavanan

**Sent:** Wednesday, February 02, 2011 10:06 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: PaCO<sub>2</sub> abstract not accepted.

Dear Colleagues,

Our PAS abstract on PaCO<sub>2</sub> in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,

Thank you for all your help,

Ambal

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**From:** Namasivayam Ambalavanan

**Sent:** Mon 11/8/2010 5:40 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Lptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,

Attached is the abstract on PaCO<sub>2</sub> SUPPORT abstract for NICHD clearance.

Thank you,

Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO<sub>2</sub> variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO<sub>2</sub> in the CPAP arm from about 33 to 34. The Max PaCO<sub>2</sub> was about the same in all groups)

Thanks,

Ambal

N. Ambalavanan MD  
Professor, Division of Neonatology  
Departments of Pediatrics, Cell Biology, and Pathology

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Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Sun 10/31/2010 6:25 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal

(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

---

**From:** Namasivayam Ambalavanan  
**Sent:** Sat 10/30/2010 8:15 PM  
**To:** Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this

hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO<sub>2</sub> and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO<sub>2</sub> and Max FiO<sub>2</sub> (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO<sub>2</sub> and days of ventilation as well as FiO<sub>2</sub> (as well as with illness severity) indicating that a higher CO<sub>2</sub> was associated with worse illness.

If one looks at the data, the time-weighted PCO<sub>2</sub> is between 48-50, and the SD of PCO<sub>2</sub> is around 10. So it seems we are already practicing permissive hypercapnia (PCO<sub>2</sub> 45-55) for the most part. Is it possible to show that targeting a even higher PCO<sub>2</sub> is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO<sub>2</sub>, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO<sub>2</sub> levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO<sub>2</sub> by CPAP/Surfactant group or by SpO<sub>2</sub> low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO<sub>2</sub> group and Max CO<sub>2</sub> in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,  
Ambal

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**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]

**Sent:** Sat 10/30/2010 4:59 PM

**To:** Namasivayam Ambalavanan

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School

6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

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**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Saturday, October 30, 2010 10:18 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook;  
NIH; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.  
Best Michele

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Fri 10/29/2010 5:28 PM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO2 in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
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**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Saturday, October 23, 2010 7:16 AM

**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO2 (using highest FiO2 on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Fri 10/22/2010 8:58 PM  
**To:** Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO2 (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO2 and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO2. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO2 were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.  
Ambal

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**From:** Michael Cotten [<mailto:cotte010@mc.duke.edu>]  
**Sent:** Fri 10/22/2010 7:57 PM  
**To:** Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon  
**Subject:** Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practitioners allow co2 to be high on min settings,,,and those kids are probably way different than kids pn high sttings or hfv who remain hypercarbic,,,

Mc

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**From:** "Namasivayam Ambalavanan" [[NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu)]  
**Sent:** 10/22/2010 03:59 PM EST  
**To:** "Wrage, Lisa Ann" <[wrage@rti.org](mailto:wrage@rti.org)>; <[ambal@uab.edu](mailto:ambal@uab.edu)>  
**Cc:** "Das, Abhik" <[adas@rti.org](mailto:adas@rti.org)>; "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>; "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; "Kennedy, Kathleen A" <[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)>;

"Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \ (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; <Michele.Walsh@UHHospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt\_laughon@med.unc.edu>

**Subject:** RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO<sub>2</sub> (especially higher PaCO<sub>2</sub> and fluctuating PaCO<sub>2</sub>) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO<sub>2</sub> is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO<sub>2</sub>, minimal PaCO<sub>2</sub>, time-weighted PaCO<sub>2</sub>, and SD of PaCO<sub>2</sub> as independent continuous variables with actual time-weighted PaO<sub>2</sub> (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO<sub>2</sub> for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO<sub>2</sub> variables with outcome, after adjustment for the other variables. We probably do not need PaCO<sub>2</sub> values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO<sub>2</sub> and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO<sub>2</sub> terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO<sub>2</sub> to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO<sub>2</sub> category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO<sub>2</sub> categories and the numbers in each CO<sub>2</sub> category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,

Ambal

N. Ambalavanan MD  
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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 22, 2010 2:48 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Wednesday, October 20, 2010 10:58 AM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.

Ambal

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Wed 10/20/2010 9:42 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the

reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.  
Thanks.  
Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <[mgantz@rti.org](mailto:mgantz@rti.org)>

Sent: Tuesday, October 19, 2010 7:29 PM

To: Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; Finer, Neil <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>

Cc: Das, Abhik <[adas@rti.org](mailto:adas@rti.org)>; Wrage, Lisa Ann <[wrage@rti.org](mailto:wrage@rti.org)>

Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5  
75th 12  
90th 21  
95th 25.5  
99th 80  
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 15, 2010 2:56 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
  - 2) I think PROM>24h is ok
  - 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
  - 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
- Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 15, 2010 1:46 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted C02 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95<sup>th</sup> %ile is 25.1 hours and the 99<sup>th</sup> %ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this

ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,  
Lisa

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**From:** Wrage, Lisa Ann  
**Sent:** Tuesday, October 05, 2010 2:45 PM  
**To:** 'Namasivayam Ambalavanan'; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.  
Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 2:38 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
My answers (>>) are below your questions (\*\*)

Ambal

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**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Tuesday, October 05, 2010 12:36 PM  
**To:** Namasivayam Ambalavanan; ambal@uab.edu  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Thank you, this is helpful, I have a few more questions (see \*\* below).  
Lisa

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**From:** Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]  
**Sent:** Tuesday, October 05, 2010 12:42 PM  
**To:** Wrage, Lisa Ann; ambal@uab.edu  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
(Abhik/Wally/Marie – your comments are also welcome)  
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

**\*\*Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.**

**>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices**

- 2) For Aim (1): determine the association of PaCO<sub>2</sub> in the first 2 weeks with outcomes, we will use PaCO<sub>2</sub> as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

**\*\*Could you please clarify how you like to summarize PaCO<sub>2</sub> over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?**

**>> I think max, min, time-weighted, and standard deviation should be ok.**

- 3) For Aims (2) and (3), to determine the association of high/low PaCO<sub>2</sub> with outcomes, we will divide infants into quartiles based on their maximum PCO<sub>2</sub> and their minimum PCO<sub>2</sub> over the first two weeks. The infants in the highest quartile of max PCO<sub>2</sub> are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO<sub>2</sub> will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia"

infants are those who in the middle two quartiles of Max PCO2 and minimum PCO2. The outcomes will be assessed in the low and high SpO2 groups in relation to PaCO2 status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

*\*\*So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO2), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO2,>> Yes. As above, I think we should have hypocapnia only, not fluctuators. Fluctuators (in both upper quartile of max PCCO2 lower quartile of min PCO2)>> Yes. Normocapnic (in middle two quartiles of max PCO2 AND min PCCO2)*

*To define Max PCO2 and Min PCO2 do you simply want me to use the maximum and minimum value of all values of PCO2 for each infant using PCO2 recorded during the 1<sup>st</sup> two weeks on the SUPP05 form?*

*>> Yes*

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO2, minPCO2, time-weighted PCO2, and SD of PCO2 as independent continuous variables with SUPPORT group assignment

*\*\*OK.*

*>>Great!*

Thanks,  
Ambal

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**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Tuesday, October 05, 2010 10:32 AM  
**To:** Namasivayam Ambalavanan; ambal@uab.edu  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these

outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 01, 2010 11:14 AM  
**To:** Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Hi Lisa, Marie,  
What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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**Fax** Office (205) 934-3100 Lab (205) 996 2333  
**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Tuesday, September 21, 2010 3:55 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, September 21, 2010 11:15 AM  
**To:** Ambal (ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Das, Abhik  
**Subject:** PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

**For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.**

November 8, 2010– Final abstracts to NICHD for clearance  
Mid-November– PAS deadline  
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
CDBPM, NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20592  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)

**From:** Kennedy, Kathleen A  
**To:** Namasivayam Ambalavanan; Shankaran, Seetha; Michael Cotten, M.D.  
**Cc:** Walsh, Michele; Abhik Das; Ganiz, Marie; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wraga, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan  
**Subject:** RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement  
**Date:** Wednesday, September 18, 2013 11:30:35 AM  
**Attachments:** Kramer (Pacifier Use RCT) 2001.pdf  
PCO2\_SUPPORT\_Aug1\_2013 (KAK).docx

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Sorry this has taken me a while. I've really been struggling with how to summarize and present this in a way that's informative and adds to what's already been published about this. (I've also been on service, out of town, etc.)

I'm still troubled by how we're handling the independent variables that were randomly allocated vs the ones that were not. The most robust assessments of the effects of different O2 sat ranges and different PaCO2 ranges would come from the primary unadjusted (except for stratification by center) analyses (looking at BPD, death/BPD, ICH, death/ICH as outcomes) according to the strata in the factorial design that should have achieved different distributions in achieved O2 sats and achieved PaCO2. Ideally you would also look at the interaction although the trial wasn't powered for this. I think we should view these analyses as the most unbiased (albeit underpowered) assessments of causal relationships. These analyses aren't much different from the analyses of secondary outcomes in the primary manuscripts for SUPPORT.

Once you turn this into an observational study of different achieved PaCO2 ranges, confounding by illness severity makes a mess of things. It doesn't make obvious logical sense to me that you're looking at PaCO2 according to achieved (rather than allocation strategy for) PaCO2 but you're evaluating the effect of O2 sats and interaction using the randomized assignment (rather than achieved distributions) for O2 sat ranges. Why can't you have categories for achieved O2 sats that are similar to the categories you derived for achieved PaCO2?

Then you could do observational analyses of the associations between categories of achieved PaCO2 and achieved O2 sat with the outcomes of interest (after adjustment for the assigned allocation). Presumably the associations here would be much stronger than the effects observed by group assignment alone. You could then conclude (similar argument to the one made by Kramer et al in the Pacifier RCT, see attached) that these findings suggest that associations observed in prior observational studies are most likely due to confounding by illness severity rather than causal relationships. I think this line of reasoning would be more provocative and interesting to reviewers and readers.

I've also added a few minor comments in the manuscript. I sent the acknowledgment email to Bill. I guess you might want to try submitting this as is. I realize it would be a lot more work to make changes as above but I think it would be viewed as more provocative and interesting.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106

Houston, TX 77030  
713 500-6708

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Thursday, August 01, 2013 1:52 PM  
**To:** Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan  
**Subject:** RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement  
**Importance:** High

Dear All,

Thank you for your comments on the previous drafts. Attached is the fifth draft of our manuscript evaluating PCO2 in SUPPORT. There are minor changes since the previous draft. The paper has been formatted for PEDIATRICS. The word count is a bit high (3075 rather than 3000), so will need a little trimming. Also attached is the Authorship Agreement – please complete and email (click the button on form to automatically email it to me) or print and fax (205-934-3100) to me. Once I hear back from anyone, if there are no further major comments, I will send to the Publications subcommittee, and then make changes in response to Publication Subcomm Reviewer comments, and then finally send for NICHD Clearance before submission.

Sincerely,  
Ambal

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**From:** Namasivayam Ambalavanan [[NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu)]  
**Sent:** Friday, July 05, 2013 11:35 AM  
**To:** Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Shankaran, Seetha; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Fourth draft of July 5, 2013

Dear All,

Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

- 1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
- 2) Some clarifications of methods and explanations in Discussion.
- 3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,  
Ambal

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, March 05, 2013 12:54 PM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis ( Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Thursday, February 21, 2013 10:37 AM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : first draft of Feb21, 2013  
**Importance:** High

Dear All,

Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)

Thank you for all your help,  
Best regards,  
Ambal

Namasivayam Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology  
University of Alabama at Birmingham

**Mailing Address:**

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Birmingham, AL 35249-7335  
**Tel Office** (205) 934 4680 *Lab* (205) 934 0751 or 996 5419  
**Fax Office** (205) 934-3100 *Lab* (205) 996 2333  
**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Wednesday, February 02, 2011 10:06 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,

Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,

Thank you for all your help,

Ambal

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**From:** Namasivayam Ambalavanan

**Sent:** Mon 11/8/2010 5:40 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptok; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,

Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.

Thank you,

Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,

Ambal

N. Ambalavanan MD

Professor, Division of Neonatology

Departments of Pediatrics, Cell Biology, and Pathology

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Tel Office (205) 934 4680 Lab (205) 934 0751 or 996 5419

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Email [ambal@uab.edu](mailto:ambal@uab.edu)

---

**From:** Namasivayam Ambalavanan

**Sent:** Sun 10/31/2010 6:25 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptok; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal

(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

---

**From:** Namasivayam Ambalavanan

**Sent:** Sat 10/30/2010 8:15 PM

**To:** Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,  
Ambal

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**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]

**Sent:** Sat 10/30/2010 4:59 PM

**To:** Namasivayam Ambalavanan

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHHospitals.org]

**Sent:** Saturday, October 30, 2010 10:18 AM

**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran

**Subject:** RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

Best Michele

---

**From:** Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]

**Sent:** Fri 10/29/2010 5:28 PM

**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal

**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh,

**Michele; Matt Laughon; Seetha Shankaran**  
**Subject:** RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO<sub>2</sub> in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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**Fax** Office (205) 934-3100 Lab (205) 996 2333  
**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Saturday, October 23, 2010 7:16 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO<sub>2</sub> (using highest FiO<sub>2</sub> on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Fri 10/22/2010 8:58 PM  
**To:** Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO<sub>2</sub> (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO<sub>2</sub> and minute

ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO<sub>2</sub>. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO<sub>2</sub> were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.  
Ambal

---

**From:** Michael Cotten [<mailto:cotte010@mc.duke.edu>]  
**Sent:** Fri 10/22/2010 7:57 PM  
**To:** Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon  
**Subject:** Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practitioners allow co2 to be high on min settings,,,and those kids are probably way different than kids on high settings or hfvs who remain hypercarbic,,,

Mc

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**From:** "Namasivayam Ambalavanan" [[NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu)]  
**Sent:** 10/22/2010 03:59 PM EST  
**To:** "Wrage, Lisa Ann" <[wrage@rti.org](mailto:wrage@rti.org)>; <[ambal@uab.edu](mailto:ambal@uab.edu)>  
**Cc:** "Das, Abhik" <[adas@rti.org](mailto:adas@rti.org)>; "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>; "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; "Kennedy, Kathleen A" <[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)>; "Laptook, Abbot" <[ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org)>; "Higgins, Rosemary (NIH/NICHD)" [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>; <[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)>; Michael Cotten; "Laughon, Matthew M" <[matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu)>  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO<sub>2</sub> (especially higher PaCO<sub>2</sub> and fluctuating PaCO<sub>2</sub>) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO<sub>2</sub> is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO<sub>2</sub>, minimal PaCO<sub>2</sub>, time-weighted PaCO<sub>2</sub>, and SD of PaCO<sub>2</sub> as independent continuous variables with actual time-weighted PaO<sub>2</sub> (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO2 for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO2 variables with outcome, after adjustment for the other variables. We probably do not need PaCO2 values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO2 and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO2 terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO2 to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO2 category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO2 categories and the numbers in each CO2 category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 22, 2010 2:48 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing

these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]

**Sent:** Wednesday, October 20, 2010 10:58 AM

**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.

**Subject:** RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.

Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]

**Sent:** Wed 10/20/2010 9:42 AM

**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.

**Subject:** RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.

Thanks.

Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

From: Gantz, Marie <[mgantz@rti.org](mailto:mgantz@rti.org)>

Sent: Tuesday, October 19, 2010 7:29 PM  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>  
Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>  
Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5  
75th 12  
90th 21  
95th 25.5  
99th 80  
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 15, 2010 2:56 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
- 2) I think PROM>24h is ok
- 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
- 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.

Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 15, 2010 1:46 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95<sup>th</sup> %ile is 25.1 hours and the 99<sup>th</sup> %ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,  
Lisa

---

**From:** Wrage, Lisa Ann

**Sent:** Tuesday, October 05, 2010 2:45 PM  
**To:** 'Namasivayam Ambalavanan'; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 2:38 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
My answers (>>) are below your questions (\*\*)

Ambal

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 12:36 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Thank you, this is helpful, I have a few more questions (see \*\* below).  
Lisa

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 12:42 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
(Abhik/Wally/Marie – your comments are also welcome)

If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

**\*\*Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.**

**>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices**

- 2) For Aim (1): determine the association of PaCO<sub>2</sub> in the first 2 weeks with outcomes, we will use PaCO<sub>2</sub> as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

**\*\*Could you please clarify how you like to summarize PaCO<sub>2</sub> over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?**

**>> I think max, min, time-weighted, and standard deviation should be ok.**

- 3) For Aims (2) and (3), to determine the association of high/low PaCO<sub>2</sub> with outcomes, we will divide infants into quartiles based on their maximum PCO<sub>2</sub> and their minimum PCO<sub>2</sub> over the first two weeks. The infants in the highest quartile of max PCO<sub>2</sub> are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO<sub>2</sub> will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO<sub>2</sub> and minimum PCO<sub>2</sub>. The outcomes will be assessed in the low and high SpO<sub>2</sub> groups in relation to PaCO<sub>2</sub> status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

**\*\*So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO<sub>2</sub>), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO<sub>2</sub>), >> Yes. As above, I think we should have hypocapnia only, not fluctuators.**

**Fluctuators (in both upper quartile of max PCO<sub>2</sub> lower quartile of min PCO<sub>2</sub>) >> Yes.**

**Normocapnic (in middle two quartiles of max PCO<sub>2</sub> AND min PCO<sub>2</sub>) >> Yes.**

**To define Max PCO<sub>2</sub> and Min PCO<sub>2</sub> do you simply want me to use the maximum and minimum value of all values of PCO<sub>2</sub> for each infant using PCO<sub>2</sub> recorded during the 1<sup>st</sup> two weeks on the SUPP05 form?**

**>> Yes**

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO<sub>2</sub>, minPCO<sub>2</sub>, time-weighted PCO<sub>2</sub>, and SD of PCO<sub>2</sub> as independent continuous variables with SUPPORT group assignment

**\*\*OK.**

**>>Great!**

Thanks,  
Ambal

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 10:32 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Dr. Ambalavanan,  
I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 01, 2010 11:14 AM  
**To:** Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie

**Subject: RE: PAS ABSTRACT**

Hi Lisa, Marie,

What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?

Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Tuesday, September 21, 2010 3:55 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, September 21, 2010 11:15 AM  
**To:** Ambal ([ambal@uab.edu](mailto:ambal@uab.edu))  
**Cc:** Wally Carlo, M.D.; Das, Abhik  
**Subject:** PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

**For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the**

**appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.**

November 8, 2010– Final abstracts to NICHD for clearance

Mid-November– PAS deadline

April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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ORIGINAL CONTRIBUTION

# Pacifier Use, Early Weaning, and Cry/Fuss Behavior

## A Randomized Controlled Trial

Michael S. Kramer, MD

Ronald G. Barr, MDCM

Suzanne Dagenais, BScN

Hong Yang, MSc

Patricia Jones, MSc, IBCLC

Luisa Ciofani, MSc, IBCLC

Frederick Jané, BA

**P**ACIFIERS HAVE BEEN AROUND for a very long time. Small clay pacifiers have been found in Cypriot graves dating back to about 1000 BC, and breast-shaped pottery nipples have been recovered from Roman graves dating from around AD 100.<sup>1,2</sup> In the early 1900s, however, pacifiers began to be condemned by the infant welfare movement. Various reformers referred to the pacifier as a product of "perverted American ingenuity," an "instrument of torture,"<sup>3</sup> and a "curse of babyhood."<sup>4</sup> More recently, clinicians and public health practitioners have raised concerns that the pacifier causes "nipple confusion" and thereby leads to early weaning.<sup>6</sup> In fact, avoidance of pacifiers constitutes step 9 of the World Health Organization/United Nations Children's Fund Baby-Friendly Hospital Initiative.<sup>7</sup>

What is the evidence of actual benefit or harm associated with pacifier use? Several observational studies published since the Baby-Friendly Hospital Initiative was developed, including studies from Brazil,<sup>8-10</sup> Sweden,<sup>11,12</sup> England,<sup>13,14</sup> New Zealand,<sup>15</sup> and the

**Context** The World Health Organization and the United Nations Children's Fund strongly discourage use of pacifiers because of their perceived interference with breastfeeding. Observational studies have reported a strong association between pacifier use and early weaning, but such studies are unable to determine whether the association is causal.

**Objectives** To test whether regular pacifier use is causally related to weaning by 3 months postpartum and to examine differences in results according to randomized intervention allocation vs observational use or nonuse of pacifiers.

**Design** Double-blind, randomized controlled trial conducted from January 1998 to August 1999.

**Setting** Postpartum unit of a university teaching hospital in Montreal, Quebec.

**Participants** A total of 281 healthy, breastfeeding women and their healthy, term singleton infants.

**Interventions** Participants were randomly allocated to 1 of 2 counseling interventions provided by a research nurse trained in location counseling. The experimental intervention (n=140) differed from the control (n=141) by recommending avoidance of pacifier use and suggesting alternative ways to comfort a crying or fussing infant.

**Main Outcome Measures** Early weaning, defined as weaning within the first 3 months, compared between groups; 24-hour infant behavior logs detailing frequency and duration of crying, fussing, and pacifier use at 4, 6, and 9 weeks.

**Results** A total of 258 mother-infant pairs (91.8%) completed follow-up. The experimental intervention increased total avoidance of pacifier use (38.6% vs 16.0% in the control group), reduced daily use (40.8% vs 55.7%), and decreased the mean number of pacifier insertions per day (0.8 vs 2.4 at 4 weeks [ $P<.001$ ]; 0.8 vs 3.0 at 6 weeks [ $P<.001$ ]; and 1.3 vs 3.0 at 9 weeks [ $P=.004$ ]). In the analysis based on randomized intervention allocation, the experimental intervention had no discernible effect on weaning at 3 months (18.9% vs 18.3% in the experimental vs control group; relative risk [RR], 1.0; 95% confidence interval [CI], 0.6-1.7), and no effect was observed on cry/fuss behavior (in the experimental vs control groups, respectively, total daily duration, 143 vs 151 minutes at 4 weeks [ $P=.49$ ]; 128 vs 131 minutes at 6 weeks [ $P=.81$ ]; and 110 vs 104 minutes at 9 weeks [ $P=.58$ ]). When randomized allocation was ignored, however, we observed a strong observational association between exposure to daily pacifier use and weaning by 3 months (25.0% vs 12.9% of the exposed vs unexposed groups; RR, 1.9; 95% CI, 1.1-3.3).

**Conclusions** We found a strong observational association between pacifier use and early weaning. No such association was observed, however, when our data were analyzed by randomized allocation, strongly suggesting that pacifier use is a marker of breastfeeding difficulties or reduced motivation to breastfeed, rather than a true cause of early weaning.

JAMA. 2001;286:322-326

www.jama.com

**Author Affiliations:** Departments of Pediatrics (Drs Kramer and Barr), Epidemiology and Statistics (Dr Kramer), and Psychiatry (Dr Barr), McGill University Faculty of Medicine; and McGill University Health Centre Research Institute (Mss Dagenais, Jones,

and Ciofani; Messrs Yang and Jané), Montreal, Quebec.

**Corresponding Author and Reprints:** Michael S. Kramer, 1020 Pine Ave W, Montreal, Quebec, Canada H3A 1A2 (e-mail: mkrame@po-box.mcgill.ca).

See also Patient Page.

United States,<sup>16</sup> have reported a significant association between pacifier use and early weaning. The question is whether such an association is causal, or whether pacifier use is a marker of breastfeeding difficulties or a mother's reduced motivation to continue breastfeeding. No physiological evidence has validated the concept of nipple confusion; an infant can apparently distinguish nutritive from non-nutritive sucking.<sup>17-20</sup> It is clear that pacifiers reduce crying in the short term<sup>21-29</sup> but no studies have assessed whether the regular use of pacifiers reduces the overall duration or frequency of crying and fussing. Such studies are important, because prescription of pacifier use could conceivably increase infant distress and thereby impair infant-parent relationships.

The major objectives of our study were to assess whether advice to avoid pacifier use and to use other modes of calming a crying or fussing infant reduces the risk of early weaning (before age 3 months) and increases the frequency or duration of crying and fussing. We also wished to assess the bias that occurs in using an observational vs an experimental design to study the effect of pacifier use on breastfeeding duration.

## METHODS

### Design

We carried out a randomized controlled trial from January 1998 to August 1999 of women giving birth at the Royal Victoria Hospital, a McGill University-affiliated maternity hospital in Montreal, Quebec. The Royal Victoria Hospital Research Ethics Board approved the study. Women who intended to breastfeed for at least 3 months and who were delivered of (vaginally or by cesarean) healthy singleton newborns of at least 37 completed weeks' gestational age and 2500 g birth weight were eligible for inclusion. They were recruited during their postpartum stay, with enrollment of at most 1 mother per room to avoid the treatment contamination that would likely occur if mothers randomized to different interventions occupied the same hospital room.

Women were stratified by parity and, if multiparous, according to whether they had breastfed previously. Randomization within each stratum was accomplished using computer-generated random numbers in blocks of 4. Women consented to randomization to 1 of 2 different breastfeeding promotion "packages" (see below); the assigned allocation was contained in an opaque envelope opened by a research nurse after consent was obtained. Based on the literature available<sup>8,9,11,15</sup> at the time we planned this trial, we estimated that a reduction in daily pacifier use from 60% to 40% would reduce the risk of weaning before age 3 months from 40% to 35%. With an  $\alpha$  level of .05 and a  $\beta$  of .10, approximately 140 infants were required per group.

### Interventions

The basic breastfeeding promotion package included in both interventions consisted of a 45-minute interview promoting breastfeeding plus an information sheet, both provided by a nurse with specialized training in lactation counseling. This interview and information focused on positioning, the importance of frequent feeding and feeding on demand, the avoidance of formula and other liquids, the management of sore nipples and breast engorgement, and provided the telephone numbers of persons and agencies whom the mother could call for answers to questions, help with difficulties, and general support. In addition, for the experimental intervention, the mother was asked to avoid pacifiers when the infant cried or fussed and to first offer the breast instead, and failing that, to try carrying and rocking the infant. In the control intervention, all options were discussed for calming the infant, including breastfeeding, carrying, rocking, and using a pacifier. The experimental vs control intervention was reinforced by the research nurse by telephone calls at 10 days and 3 weeks postpartum.

### Ascertainment of Outcomes

We asked mothers to complete a validated behavior diary<sup>26,27</sup> on 3 consecu-

tive days, including 2 weekdays and 1 weekend day, when their infants were 4, 6, and 9 weeks of age. This diary provides exhaustive and mutually exclusive indicators of infant behaviors, including the frequency and duration of all crying and fussing episodes. Periods of unsoothable crying are recorded separately. An indicator for each pacifier insertion was added to a previous version of the instrument.<sup>28</sup> Study mothers were interviewed at 3 months by a research assistant who was blinded to the intervention status of the mother. The assistant asked whether the mother was still breastfeeding. If so, the research assistant also asked about the frequency of breastfeeding and whether the infant was receiving other foods in addition to breast milk. If the infant was no longer breastfeeding, the research assistant asked the age at which the infant was weaned (ie, when breastfeeding was permanently discontinued) and the reasons for weaning. In addition, she asked about the average frequency of pacifier use over the infant's first 3 months of life.

### Statistical Analysis

The primary outcome, early weaning (weaning within the first 3 months), was compared between the 2 randomized intervention groups using the relative risk (RR) and the 95% confidence interval (CI). We also carried out a multiple logistic regression analysis to ensure that the crude RR was not confounded by observed differences in baseline characteristics. Secondary outcomes included the frequency (number of episodes per day) and total duration (minutes per day) of crying or fussing and the duration of unsoothable crying (minutes per day); these outcomes were compared using 2-tailed *t* tests, with  $P < .05$  indicating statistical significance. All analyses were based on randomized intervention allocation in the mothers who completed the study, because no outcomes could be ascertained in those who were lost to follow-up.

To contrast the results obtained for the primary outcome based on randomized intervention allocation with those obtained if randomized allocation was

PACIFIERS, WEANING, AND CRYING

ignored, we also analyzed the data as if we had done an observational study. This analysis compared the RR and 95% CI in groups who had ever (vs never) been exposed to a pacifier and in groups who were (vs were not) exposed on a daily basis.

All statistical analyses were carried out using SAS version 6.12 (SAS Institute, Cary, NC).

**RESULTS**

Of the 281 mothers randomized, 258 (91.8%; 127 experimental and 131 control) completed the study (FIGURE). TABLE 1 compares the baseline charac-

teristics of these 258 mothers. Maternal age and education, infant birth weight, English-language interview, maternal employment outside the home, parity, and previous breastfeeding experience were very similar in the 2 groups, although a slightly lower proportion of experimental mothers were married and a slightly higher proportion smoked during pregnancy. The only differences in baseline characteristics observed among the 23 mothers originally randomized who did not complete the study were a lower proportion who were married (69.6% vs 81.4%), a higher proportion who smoked (26.1% vs 13.0%), and, paradoxically, a lower proportion who worked outside the home (43.5% vs 76.0%).

As shown in TABLE 2, the intervention succeeded in substantially changing pacifier use; 38.6% of mothers in the experimental group totally avoided pacifier use, compared with 16.0% in the control group, for a statistically significant RR of 2.4. Daily use of pacifiers was substantially reduced in the experimental group (40.8% vs the control group (55.7%), for a statistically significant 30% relative reduction. The diary data indicated a large and highly sig-

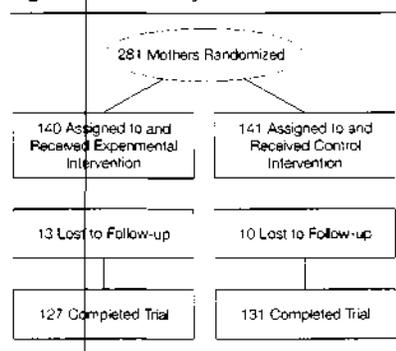
nificant reduction in the mean number of pacifier insertions per day in the experimental group at 4, 6, and 9 weeks of age.

We first analyzed the results for early weaning based on randomized allocation. Among the 258 infants whose mothers completed the study, 18.9% of those in the experimental group were weaned prior to age 3 months vs 18.3% of those in the control group (RR, 1.0; 95% CI, 0.6-1.7). The results for exclusive breastfeeding were similar: 63.8% of infants in the experimental group had discontinued exclusive breastfeeding by age 3 months vs 66.4% of those in the control group (RR, 1.0; 95% CI, 0.8-1.1). To ensure that these negative experimental results were not confounded by small baseline differences in marital status or smoking, we carried out a logistic regression analysis to control for these differences. The adjusted odds ratio and 95% CI for weaning by age 3 months (1.0 [0.5-1.9]) was virtually unchanged from the crude odds ratio (1.0 [0.6-1.9]).

In contrast, the observational analysis of early weaning yielded very different results. When exposure was based on daily pacifier use, 25.0% of exposed infants were weaned prior to age 3 months vs 12.9% of unexposed infants (RR, 1.9; 95% CI, 1.1-3.3). When exposure was based on whether the infants had ever used a pacifier, the corresponding proportions weaned before age 3 months were 21.3% vs 11.4% (RR, 1.9; 95% CI, 0.9-3.8). Observational associations with exclusive breastfeeding were weaker but statistically significant. For exposure based on daily pacifier use, 72.6% of exposed infants vs 58.3% of unexposed infants had discontinued exclusive breastfeeding before age 3 months (RR, 1.2; 95% CI, 1.04-1.5). For exposure based on ever using pacifiers, the corresponding values were 69.1% vs 54.3% (RR, 1.3; 95% CI, 1.01-1.6).

Only 183 (70.9%), 156 (60.5%), and 148 (57.4%) of the mothers returned the infant behavior diaries at 4, 6, and 9 weeks, respectively, with no differences between experimental

**Figure.** Flow of Study



**Table 1.** Baseline Comparison of Experimental and Control Groups

Variable	Experimental (n = 127)	Control (n = 131)
Age, mean (SD), y	31.6 (4.5)	31.5 (4.9)
Education, mean (SD), y	16.1 (3.0)	16.0 (3.2)
Birth weight, mean (SD), g	3457 (427)	3524 (415)
English-language interview, %	66.1	66.2
Married, %	78.7	84.0
Employed outside home, %	77.2	74.8
Smoked during pregnancy, %	15.3	10.8
Primiparous, %	47.2	47.3
Previous breastfeeding (multiples), %	97.0	95.6

**Table 2.** Effect of Intervention on Pacifier Use\*

Pacifier Use	Experimental	Control	RR (95% CI) or P Value†
Total avoidance, %	38.6	16.0	2.4 (1.5-3.8)
Daily use, %	40.8	55.7	0.7 (0.6-0.95)
Mean uses per day			
4 wk	0.8	2.4	P < .001
6 wk	0.8	3.0	P < .001
9 wk	1.3	3.0	P = .004

\*RR indicates relative risk; CI, confidence interval.  
†P values based on 2-tailed t tests.

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and control groups. TABLE 3 shows the results (analyzed by randomized intervention allocation) for cry/fuss behavior, including daily frequency, ie, the number of episodes of crying (including unsoothable crying) or fussing per day, total daily duration of all crying and fussing, and total daily duration of unsoothable crying. Cry/fuss frequency was slightly lower in the experimental group at 4 and 6 weeks, but almost identical in the 2 groups at 9 weeks. The total duration of crying and fussing was similar in the 2 groups at all 3 ages, as was the total duration of unsoothable crying.

Because of the substantial nonresponse rate to the diary completion, we compared baseline characteristics of those who did not complete diaries in the experimental and control groups at 4, 6, and 9 weeks postpartum. The results (TABLE 4) indicate that nonresponders at all 3 time periods were younger, less educated, and less likely to be married. As shown in Table 1, however, these characteristics were similar between the experimental and control groups (which was also true when stratified by diary response at all 3 time periods), and thus the differences between responders and nonresponders are highly unlikely to have biased the effects of intervention on cry/fuss behavior.

**COMMENT**

Our experimental intervention succeeded in substantially reducing pacifier use, yet it had no significant effect

on cry/fuss behavior at ages 4, 6, or 9 weeks. Similarly, our intervention had no effect on the risk of weaning before age 3 months. Despite these negative results, however, pacifier use was strongly associated with the risk of early weaning in observational analyses, similar to results reported in previous observational studies.<sup>8-16</sup> This combination of findings leads us to conclude that pacifier use is a marker of breastfeeding difficulties or reduced motivation to breastfeed, rather than a true cause of early weaning. We reported an identical contrast between experimental and observational results in an earlier trial of in-hospital formula supplementation of breastfed infants.<sup>29,30</sup>

Although we found no evidence that pacifier use is harmful for breastfeeding, we also detected no beneficial effects on infant crying and fussing. Thus the nonpacifier soothing methods (breastfeeding, carrying, and rocking)

advocated in our experimental intervention appear adequate. Nonetheless, the absence of a causal link between pacifier use and early weaning should lead breastfeeding promotion programs and international agencies to reexamine their staunch opposition to pacifiers.

Like any study, ours has limitations. A larger sample size would be required to exclude a small increased risk of early weaning, as shown by the width of our confidence interval for that outcome. We deliberately chose an experimental intervention that could be feasibly implemented on a large scale if it was successful in reducing the risk of early weaning, but our results cannot be generalized to more potent interventions to avoid pacifier use. Data on pacifier use were based on maternal self-report, but the recording of use from the written behavior diaries at 4, 6, and 9 weeks and the telephone interview at 3 months were consistent in showing

**Table 3.** Effect of Intervention on Cry/Fuss Behavior

Outcome	Experimental	Control	P Value*
<b>4 Weeks (n = 183)</b>			
Frequency, episodes per day	6.3	7.7	.03
Total duration, min/d	143	151	.49
Unsoothable crying, min/d	8.4	9.1	.77
<b>6 Weeks (n = 156)</b>			
Frequency, episodes per day	6.7	7.7	.19
Total duration, min/d	128	131	.81
Unsoothable crying, min/d	6.1	5.2	.66
<b>9 Weeks (n = 148)</b>			
Frequency, episodes per day	6.7	6.8	.88
Total duration, min/d	110	104	.58
Unsoothable crying, min/d	3.1	3.6	.78

\*P values based on 2-tailed t tests.

**Table 4.** Comparison of Baseline Characteristics Between Responders and Nonresponders for Diary Completion at 4, 6, and 9 Weeks

Variable	4 Weeks		6 Weeks		9 Weeks	
	Responders (n = 183)	Nonresponders (n = 98)	Responders (n = 156)	Nonresponders (n = 125)	Responders (n = 148)	Nonresponders (n = 133)
Age, mean (SD), y	31.9 (4.3)	30.3 (5.2)	32.2 (4.1)	30.3 (5.2)	32.1 (4.0)	30.5 (5.3)
Education, mean (SD), y	16.3 (2.9)	15.2 (3.3)	16.3 (3.0)	15.4 (3.1)	16.3 (2.9)	15.5 (3.3)
Birth weight, mean (SD), g	3523 (416)	3421 (413)	3506 (406)	3465 (431)	3493 (414)	3482 (422)
English-language interview, %	64.8	70.4	65.8	68.0	66.0	67.7
Married, %	84.7	72.4	83.3	76.8	85.1	74.4
Employed outside home, %	72.7	74.5	73.1	73.6	70.9	75.9
Smoked during pregnancy, %	16.8	12.6	12.9	15.6	14.3	13.8
Primiparous, %	46.4	51.0	46.8	49.6	48.6	47.4
Previous breastfeeding (multiples), %	95.9	97.9	96.4	96.8	96.1	97.1

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large differences between the 2 intervention groups. Maternal self-report has been the basis of data on pacifier use in all previous studies; like ours, these studies have resulted in strong and statistically significant observational associations between pacifier use and early weaning. Finally, we had an approximately 40% nonresponse rate to the diary completion, with a potential for selection bias in our analyses of cry/fuss behavior. The characteristics of responders and nonresponders were virtually identical in the experimental and control groups, however, and thus such a bias seems unlikely.

Breastfeeding, pacifier use, and infant cry/fuss behavior are complex behaviors heavily influenced by cultural, motivational, and psychological factors that are extremely difficult to measure, and hence to control for, in an observational study. As we have previously discussed,<sup>30</sup> these potent factors are likely to lead to residual confounding and reverse causality bias in observational studies of the pacifier-weaning association. Unlike recent results suggesting that observational studies of pharmacological and surgical treatments can yield valid results,<sup>31,32</sup> valid assessment of the effects of be-

havioral interventions on behavioral outcomes appears to require the bias reduction provided by randomized trials.

**Author Contributions:** Study concept and design: Kramer, Barr, Jones, Ciofani.  
**Acquisition of data:** Dagenais, Jané.  
**Analysis and interpretation of data:** Kramer, Barr, Yang, Jané.  
**Drafting of the manuscript:** Kramer.  
**Critical revision of the manuscript for important intellectual content:** Kramer, Barr, Dagenais, Ciofani.  
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**Study supervision:** Kramer, Barr.  
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**Title:**

**Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

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**Short Title: PaCO<sub>2</sub> and IVH**

**Abbreviations:** BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

**Keywords:** Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

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**Word count:** abstract: 250; text of manuscript: 3075 (Introduction, Methods, Results, and Discussion).

**What's known on this subject:** Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

**What this study adds:** Higher  $\text{PaCO}_2$  and greater fluctuation in  $\text{PaCO}_2$  were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of  $\text{PaCO}_2$  with  $\text{FiO}_2$  and days of ventilation support higher maximum  $\text{PaCO}_2$  as a marker of illness severity in extremely premature infants

**ABSTRACT:**

**Objective:** To determine the association of PaCO<sub>2</sub> with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO<sub>2</sub> targets of 85-89% vs 91-95%) and ventilation strategies. Five PaCO<sub>2</sub> variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO<sub>2</sub>], hypocapnic [lowest quartile of Min PaCO<sub>2</sub>], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO<sub>2</sub>]). Adjusted and unadjusted analyses compared PaCO<sub>2</sub> variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all p <0.0001). A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> (r,0.55, p<0.0001) & ventilator days (r,0.61, p<0.0001). **Conclusions:** Higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). Correlation of PaCO<sub>2</sub> with FiO<sub>2</sub> and ventilator days supports higher Max PaCO<sub>2</sub> as a marker of illness severity.

(Abstract Word Count = 250)

## MANUSCRIPT TEXT

### INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)<sup>1</sup>, periventricular leukomalacia (PVL)<sup>2, 3</sup>, bronchopulmonary dysplasia (BPD)<sup>4</sup>, and subsequent neurodevelopmental impairment (NDI)<sup>5</sup>. Increased  $\text{PaCO}_2$  increases cerebral blood flow,<sup>6-8</sup> while decreased  $\text{PaCO}_2$  reduces cerebral blood flow and electrical activity, while increasing cerebral fractional oxygen extraction.<sup>9</sup> We have previously shown that both high and low  $\text{PaCO}_2$  levels and wide fluctuations in  $\text{PaCO}_2$  are associated with a higher risk of severe IVH (sIVH; IVH Grades III or IV).<sup>1</sup> Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.<sup>2, 3, 10</sup>

Cerebral blood flow decreases slightly with increased oxygenation<sup>8</sup> but the interactions between  $\text{PaCO}_2$  and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher  $\text{PaCO}_2$ <sup>4, 11, 12</sup> as well as a lower oxygen saturation ( $\text{SpO}_2$ ) target,<sup>13</sup> permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher  $\text{PaCO}_2$  (permissive hypercapnia) as well as a lower  $\text{PaO}_2$  (targeting a lower  $\text{SpO}_2$  range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation and compared outcomes in infants randomly assigned to  $\text{SpO}_2$  targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a  $\text{PaCO}_2 > 65$  mm Hg permitted intubation, while a  $\text{PaCO}_2 < 65$  mm Hg with a  $\text{pH} > 7.20$  was a mandatory extubation criterion) or intubation and surfactant within 1 hour after birth (a

PaCO<sub>2</sub><50 mm Hg with a pH>7.30 was a mandatory extubation criterion).<sup>13, 14</sup> Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP (higher PaCO<sub>2</sub> target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by postnatal day 7. In the lower SpO<sub>2</sub> target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes although a trend for reduced BPD (physiological definition)<sup>15, 16</sup> was noted in the lower SpO<sub>2</sub> target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).<sup>13</sup> However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups.<sup>17</sup>

It is possible that clinical outcomes that are not significantly different by SpO<sub>2</sub> target groups might be different when the combination of PaCO<sub>2</sub> and SpO<sub>2</sub> is analyzed. We hypothesized that both extremes of PaCO<sub>2</sub> would be associated with severe IVH, and that effect modification of SpO<sub>2</sub> will be observed, with hypercapnia associated with sIVH in the low but not high SpO<sub>2</sub> group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO<sub>2</sub>, and that higher PaCO<sub>2</sub> will be associated with a higher risk of NDI.

## **PATIENTS AND METHODS**

### **Patient characteristics:**

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.<sup>13, 14</sup> Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical

outcomes, and treatment. The characteristics of this population<sup>13</sup> and of the follow-up cohort<sup>17</sup> have been previously reported.

#### **PaCO<sub>2</sub> variables**

Five PaCO<sub>2</sub> variables were defined for this observational study, using routine blood gas measurements not governed by study protocol. Data were collected on all PaCO<sub>2</sub> from blood gases done at 3 daily time points closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max PaCO<sub>2</sub>), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO<sub>2</sub> was calculated as described previously:<sup>1</sup> briefly, the sum of all PaCO<sub>2</sub> values multiplied by the corresponding time interval (from previous blood gas) was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5<sup>th</sup>-95<sup>th</sup> centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO<sub>2</sub> over days 1-14 into quartiles. Infants with minimum PaCO<sub>2</sub> in the lowest quartile who were not also in the highest quartile of maximum PaCO<sub>2</sub> were then categorized as 'hypocapnic'. Infants with maximum PaCO<sub>2</sub> levels in the highest quartile who were not also in the lowest quartile of minimum PaCO<sub>2</sub> level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO<sub>2</sub> and the highest quartile of maximum PaCO<sub>2</sub> were categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO<sub>2</sub> level fall in quartiles 2-4 and maximum PaCO<sub>2</sub> levels fall in quartiles 1-3 were categorized as 'normocapnic'.

**Comment [KKA1]:** I think this might be confusing for people not involved in multicenter RCTs. Data were not collected on all PaCO<sub>2</sub>s. I would say "For postnatal days 1-14, the PaCO<sub>2</sub>s collected closest to 8 am, 4 pm and midnight were recorded. From these data, the minimum level, maximum... were derived." It also looks like we only used or only collected the PaCO<sub>2</sub> measurements on days 1,3,7 and 14. If that's the case, I think this is misleading because it seems to say that PaCO<sub>2</sub>s were recorded 3 times every day between days 1 and 14.

#### **Other variables**

Maternal hypertension was defined as pregnancy induced hypertension (PIH). Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum  $\text{FiO}_2$  was defined as the maximum of  $\text{FiO}_2$  at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as  $\text{FiO}_2 > 0.4$  and mechanical ventilation for 8+ hours in the 1<sup>st</sup> 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),<sup>18</sup> and BPD was defined using the physiologic definition at 36 w PMA.<sup>15, 16</sup> Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.<sup>17</sup>

**Comment [KKA2]:** Does this mean the maximum in the interval between birth and that day or the maximum on that particular day?

#### Statistical Analysis

The  $\text{PaCO}_2$  and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the  $\text{PaCO}_2$  and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ( $p < .05$ ) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis-generating goals of this observational study, no adjustments were made for multiple comparisons.

**Comment [KKA3]:** This seems inconsistent to me. In the Introduction, you mention several hypotheses that were tested.

Adjusted results for the maximum  $\text{PaCO}_2$ , the 4 level  $\text{PaCO}_2$  categorical variable, as well as time-weighted  $\text{PaCO}_2$  were obtained using generalized estimating equation (GEE) models for binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same

treatment arm in SUPPORT. Variables included in models along with the PaCO<sub>2</sub> variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes, and center. SUPPORT treatment group variables (High/Low SpO<sub>2</sub>; CPAP/ventilator) were also included in models that contained maximum PaCO<sub>2</sub> and the 4 level PaCO<sub>2</sub> variable. Interactions of these PaCO<sub>2</sub> and treatment group variables were also included to assess if the effect of PaCO<sub>2</sub> varied by treatment group. A variable for actual median SpO<sub>2</sub> in the first 14 days was included in the model that contained time-weighted PaCO<sub>2</sub>. The interaction of these two variables was included to assess if the effect of time-weighted PaCO<sub>2</sub> varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

## RESULTS

### Adjusted analysis for Severe IVH/Death (Table 1):

Maximum PaCO<sub>2</sub> was significantly associated with higher odds of sIVH/death (OR 1.39, 95% CI 1.27-1.53 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg, p <0.0001). No interaction was found between PaCO<sub>2</sub> category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (High or Low SpO<sub>2</sub>), but the interaction term for time-weighted PaCO<sub>2</sub> and median SpO<sub>2</sub> in the first 14 days was significant (p<0.05), with a higher OR associated with a lower median SpO<sub>2</sub> (OR of 1.6 for median SpO<sub>2</sub> of 91, 1.44 for SpO<sub>2</sub> of 92, 1.30 for SpO<sub>2</sub> of 93, 1.18 for SpO<sub>2</sub> of 94) indicating that a higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

**Comment [KKA4]:** It seems to me that SUPPORT group assignment should be included in each of the models. The analysis by group assignment is really the only way to evaluate a causal relationship between high vs low PaCO<sub>2</sub> and high vs low O<sub>2</sub> sat and the interaction. If these variables are not important predictors in the analysis of the association between other predictors and outcome variables, they could be dropped from the model but they should at least be considered. All of the other variables (achieved PaCO<sub>2</sub> categories) should be viewed as associations that reflect illness severity rather than causal associations.

Other variables associated ( $p < 0.05$ ) with sIVH/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for BPD/Death (Table 2):

Maximum PaCO<sub>2</sub> (OR 1.57, 95% CI 1.41-1.75 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 2.41, 95% CI 1.89-3.09 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of BPD/death. The interaction term between PaCO<sub>2</sub> category and treatment group (High or Low SpO<sub>2</sub>) was significant for fluctuators ( $p = 0.006$ ), with the OR for fluctuators in the High SpO<sub>2</sub> group being 7.4, as compared to 1.18 for the low SpO<sub>2</sub> group.

Other variables associated ( $p < 0.05$ ) with BPD/death included: lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (Table 3):

Maximum PaCO<sub>2</sub> (OR 1.38, 95% CI 1.25-1.52 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 1.44, 95% CI 1.09-1.90 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of NDI/death. No significant interactions were noted between PaCO<sub>2</sub> category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (reference group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with NDI/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for Death before discharge (Table 4):

Maximum PaCO<sub>2</sub> (OR 1.36, 95% CI 1.22-1.51 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) was associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (reference

group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with death before discharge included: lower birth weight, male gender, absence of PIH, and center.

As higher maximum PaCO<sub>2</sub> may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum FiO<sub>2</sub>, days of mechanical ventilation, and severe illness), correlations of maximum PaCO<sub>2</sub> with maximum FiO<sub>2</sub>, days of ventilation, and severe illness (as previously defined) were calculated. Maximum PaCO<sub>2</sub> was positively correlated with both maximum FiO<sub>2</sub> (Spearman correlation coefficient = 0.55,  $p < 0.0001$ ) and days of ventilation (Spearman correlation coefficient = 0.61,  $p < 0.0001$ ). There was also a significant difference in PaCO<sub>2</sub> level by infants defined as having severe illness (median maximum PaCO<sub>2</sub>=78) vs. infants having no severe illness (median maximum PaCO<sub>2</sub>=61),  $p < 0.0001$ .

**Unadjusted Results (Supplemental Tables 1-4):**

All PaCO<sub>2</sub> variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in PaCO<sub>2</sub> as compared to those without sIVH. Maximum PaCO<sub>2</sub> demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum PaCO<sub>2</sub> between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted PaCO<sub>2</sub> were statistically highly significant ( $p < 0.0001$ ) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted

PaCO<sub>2</sub> compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

## DISCUSSION

We found that extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO<sub>2</sub> in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO<sub>2</sub>, days of ventilation, and severe illness). A higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> and not in the low SpO<sub>2</sub> group.

Our study has the limitation that infants in the SUPPORT trial<sup>13, 14</sup> were not primarily randomized to different specific PaCO<sub>2</sub> ranges as in the randomized trials of permissive hypercapnia<sup>4, 12, 19</sup> but to interventions (Early CPAP vs. intubation/surfactant) with different PaCO<sub>2</sub> goals. Data on corresponding ventilator settings and oxygenation index are not available to determine if reduction of PaCO<sub>2</sub> using higher ventilator settings was associated with better outcome in the SUPPORT trial. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Eighteen to 22 month follow-up was achieved in most infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups, probably because randomization in this trial most likely led to a similar range of PaCO<sub>2</sub> in both SpO<sub>2</sub> groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in

PaCO<sub>2</sub> secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.<sup>14</sup> An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (high or low SpO<sub>2</sub> target), in order to distinguish illness severity and effects of treatment group allocation (e.g. higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO<sub>2</sub> levels and wide fluctuations in PaCO<sub>2</sub> are associated with an increased risk of sIVH.<sup>1</sup> The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO<sub>2</sub> were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO<sub>2</sub>. As maximum PaCO<sub>2</sub> was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO<sub>2</sub> had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average PaCO<sub>2</sub> in combination with a lower SpO<sub>2</sub> being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) PaCO<sub>2</sub> even in infants without severe IVH was ≥48 mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the "permissive hypercapnia" range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.<sup>12</sup> Our data indicate clinical practices in academic centers have evolved to maintain PaCO<sub>2</sub> in the permissive hypercapnia

range. However, as the maximum PaCO<sub>2</sub> exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO<sub>2</sub> within this narrow range is difficult.

A higher maximum and time-weighted PaCO<sub>2</sub> and a greater magnitude of fluctuation in PaCO<sub>2</sub> were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher PaCO<sub>2</sub> rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO<sub>2</sub> elimination for a given minute ventilation, due to a higher alveolar CO<sub>2</sub> (P<sub>A</sub>CO<sub>2</sub>). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing PaCO<sub>2</sub>, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.<sup>4, 11, 12, 19</sup> In the largest randomized trial of permissive hypercapnia to date, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group (p<0.01).<sup>4</sup> An interesting finding in the present study was that greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> but not in the low SpO<sub>2</sub> group. It is speculated that higher oxygen exposure in the high SpO<sub>2</sub> group may interact with volutrauma/atelectrauma associated with fluctuating PaCO<sub>2</sub> possibly increasing the risk for BPD/death.

Maximum PaCO<sub>2</sub> was also significantly associated with higher NDI/death, confirming our previous single-center study.<sup>5</sup> This association may be secondary to maximum PaCO<sub>2</sub> being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.<sup>20</sup> Alterations in PaCO<sub>2</sub> may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO<sub>2</sub><sup>6-8</sup> may result in sIVH<sup>1</sup> and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO<sub>2</sub><sup>9</sup> may lower white matter perfusion and result in periventricular leukomalacia (PVL).<sup>2, 3, 10</sup> Brain injury associated with extremes of PaCO<sub>2</sub> may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.<sup>21, 22</sup>

In conclusion, our work demonstrates that maximum PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, maximum PaCO<sub>2</sub> may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.

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**Table 1:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of severe IVH/death

PaCO <sub>2</sub> Variable	Adjusted Odds Ratio (95% CI)	p-value
<b>Max PaCO<sub>2</sub></b> (per 10 mm Hg)	1.39 (1.27-1.53)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.11 (0.73-1.67)	0.63
<b>Hypercapnic</b>	2.60 (1.77-3.82)	<0.0001
<b>Fluctuator</b>	2.81 (1.68-4.72)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub>**</b> (per 10 mm Hg)		
<b>Median SpO<sub>2</sub>=91</b>	1.60 (1.17-2.17)	0.003
<b>Median SpO<sub>2</sub>=94</b>	1.18 (0.85-1.62)	0.32

\*\* interaction term for time-weighted PaCO<sub>2</sub> x Median SpO<sub>2</sub> in the first 14 days was significant (p=0.043) indicating that the effect of time-weighted PaCO<sub>2</sub> depended on level of Median SpO<sub>2</sub>.

**Table 2:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of BPD/death

PaCO <sub>2</sub> Variable	Adjusted Odds Ratio (95% CI)	p-value
Max PaCO <sub>2</sub> (per 10 mm Hg)	1.57 (1.41-1.75)	<0.0001
<b>PaCO<sub>2</sub> Category: <u>High SpO<sub>2</sub></u></b>		
Hypocapnic	0.73 (0.46-1.16)	0.18
Hypercapnic	2.54 (1.41-4.60)	0.002
Fluctuator	7.4 (2.6-21.0)	0.0002
Normocapnic	REFERENCE	-
<b><u>Low SpO<sub>2</sub></u></b>		
Hypocapnic	1.01 (0.63-1.63)	0.96
Hypercapnic	3.38 (1.93-5.93)	<0.0001
Fluctuator	1.18 (0.51-2.70)	0.70
Normocapnic	REFERENCE	-
Time weighted PaCO <sub>2</sub> (per 10 mm Hg)	2.41 (1.89-3.09)	<0.0001

\*\* interaction term for PaCO<sub>2</sub> category x treatment group (High or Low SpO<sub>2</sub>) was significant for Fluctuators

**Table 3:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of NDI/death

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.38 (1.25-1.52)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.03 (0.69-1.53)	0.90
<b>Hypercapnic</b>	2.69 (1.82-3.96)	<0.0001
<b>Fluctuator</b>	3.07 (1.84-5.12)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub> (per 10 mm Hg)</b>	1.44 (1.09-1.90)	0.009

**Table 4:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of death before discharge

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.36 (1.22-1.51)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	0.90 (0.54-1.50)	0.07
<b>Hypercapnic</b>	2.47 (1.61-3.77)	<0.0001
<b>Fluctuator</b>	1.88 (1.03-3.43)	0.04
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.28 (0.94-1.74)	0.12

**Supplemental Tables**

**Supplemental Tables:**

**Table 1. Bivariate analyses for Severe IVH, and for Death or Severe IVH**

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
PaCO <sub>2</sub> , level	minimum #	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
PaCO <sub>2</sub> , level	maximum #	163	1098		325	971	
	Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , deviation	standard #	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , weighted	time- #	163	1098		325	971	
	Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
PaCO <sub>2</sub> category:	#	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
	# (%)			<0.0001			<0.0001
Hypocapnic		30 (18.4)	205 (18.7)		48 (14.8)	189 (19.5)	
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65(39.9)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	164	1106		335	979	
	High O <sub>2</sub> , # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO <sub>2</sub> DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race:	# (%)						
NH Black		55 (33.5)	421 (38.1)	0.016	112 (33.4)	376 (38.4)	0.09
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	

Characteristic			Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)		55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)		55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96
HTN, induced	pregnancy #		155	1041		317	920	
	Yes, # (%)		9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#		160	1083		319	964	
	Yes, # (%)		38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#		164	1105		334	979	
	Yes, # (%)		158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#		164	1105		334	978	
	Yes, # (%)		49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#		164	1106		335	979	
	Yes, # (%)		10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#		164	1106		309	979	
	Yes, # (%)		60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#		164	1106		335	979	
	Yes, # (%)		57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>	
PaCO <sub>2</sub> , level	minimum	#	441	659		639	659	
		Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
		Median, IQR	33 (29-37)	34 (30-38)	0.015	33 (29-38)	34 (30-38)	0.25
PaCO <sub>2</sub> , level	maximum	#	441	659		639	659	
		Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
		Median, IQR	72 (64-83)	60 (50-69)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
PaCO <sub>2</sub> , deviation	standard	#	438	642		625	642	
		Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
		Median, IQR	9.8 (7.8- 11.8)	8.0(5.7-9.9)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
PaCO <sub>2</sub> , weighted	time-	#	441	659		639	659	
		Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
		Median, IQR	51 (47.3- 54.3)	46.2 (41.1- 50.4)	<0.0001	51.2 (47.2- 55.2)	46.2 (41.1- 50.4)	<0.0001
PaCO <sub>2</sub> category:	#	441	659		639	659		
Hypocapnic	# (%)	78 (17.7)	138 (20.9)	<0.0001	100 (15.7)	138 (20.9)	<0.0001	
Hypercapnic		101 (22.9)	59 (9.0)		170 (26.6)	59 (9)		
Fluctuator		48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)		
Normocapnic		214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)		
Treatment: CPAP or Surfactant group	#	442	666		650	666		
	CPAP, (%)	#	223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	442	666		650	666	
	High O <sub>2</sub> , # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO <sub>2</sub> DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	0.013	221 (34)	268 (40.2)	0.02
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	0.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
1 minute Apgar < 3	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
5 minute Apgar < 3	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
Prophylactic indomethacin	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
Vaginal delivery	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	0.004	193 (29.7)	240 (36.0)	0.01

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
PaCO <sub>2</sub> , level	minimum	#	98	872		346	872
		Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)
		Median, IQR	31 (26-36)	33 (30-38)	0.001	33 (28-38)	33 (30-38)
PaCO <sub>2</sub> , level	maximum	#	98	872		346	872
		Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)
		Median, IQR	74 (65-88)	64 (54-74)	<0.0001	76 (66-88)	64 (54-74)
PaCO <sub>2</sub> , deviation	standard	#	98	853		335	853
		Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)
		Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)
PaCO <sub>2</sub> , weighted	time-	#	98	872		346	872
		Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)
		Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)
PaCO <sub>2</sub> category:	#	98	872		346	872	
Hypocapnic	# (%)	22 (22.5)	171 (19.6)	<0.0001	51 (14.7)	171 (19.6)	<0.0001
Hypercapnic		25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)		135 (39.0)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	98	878		356	878	
	High O <sub>2</sub> , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO <sub>2</sub> DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<0.0001	734 (621-870)	850 (710-995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race:	# (%)						
NH Black		37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
NH White		37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other		3 (3.1)	30 (3.4)		14 (3.9)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, induced pregnancy	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 (26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
PaCO <sub>2</sub> , maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
PaCO <sub>2</sub> category:	#	227	991	
Hypocapnic	# (%)	26 (11.5)	196 (19.8)	<0.0001
Hypercapnic		82 (36.1)	140 (14.1)	
Fluctuator		29 (12.8)	64 (6.5)	
Normocapnic		90 (39.7)	591 (59.6)	
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	237	997	
	High O <sub>2</sub> , # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO <sub>2</sub> DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race:	# (%)			
NH Black		77(32.5)	381 (38.2)	0.26
NH White		96 (40.5)	397 (39.8)	
Hispanic		53 (22.4)	186 (18.7)	
Other		11 (4.6)	33 (3.3)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	Yes, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Kaeser, Lisa (NIH/NICHD) [E]  
**Sent:** Monday, September 16, 2013 12:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013  
**Attachments:** carome.091613.docx

Here's what I'm sending back, in substitution for what the department's draft.

L

*Lisa Kaeser, J.D.  
Director, Office of Legislation and Public Policy  
Eunice Kennedy Shriver National Institute  
of Child Health and Human Development/NIH  
31 Center Drive, MSC 2425  
Building 31, Room 2A03  
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301-496-0536  
kaeserl@mail.nih.gov*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, September 16, 2013 9:10 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]  
**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013

Hi

I spoke to Lisa – thought (b)(5) the response is really directed for the TOP Trial.

Also – there are a few items of interest from the Public Comment page from the August 28 meeting:

<http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0075>

<http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0074>

I also attached the AAP letter that went to OHRP.

Happy to discuss further

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Guttmacher, Alan (NIH/NICHD) [E]

**Sent:** Friday, September 13, 2013 2:28 PM

**To:** Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013

Okay, then.

Alan E. Guttmacher, M.D.

Director

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

National Institutes of Health

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url: [nichd.nih.gov](http://nichd.nih.gov)

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**From:** Kaeser, Lisa (NIH/NICHD) [E]

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**To:** Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013

Found it. Apparently, it is a (b)(5)

(b)(5)

L

*Lisa Kaeser, J.D.*

*Director, Office of Legislation and Public Policy*

*Eunice Kennedy Shriver National Institute*

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---

**From:** Guttmacher, Alan (NIH/NICHD) [E]

**Sent:** Friday, September 13, 2013 1:58 PM

**To:** Kaeser, Lisa (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013

Is this accurate in terms of OHRP's second letter?

(b)(5)

(b)(5)

Alan

**From:** Kaeser, Lisa (NIH/NICHD) [E]  
**Sent:** Friday, September 13, 2013 1:39 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: WF 324629 - Round 1 Clearance due by COB 09/16/2013  
**Importance:** High

Hi – We have received this draft response from Secretary Sebelius to Public Citizen for clearance (first attachment). Basically, it states that the (b)(5)

(b)(5)

Could you please let me know if you have any issues with the response? We need to clear/comment by COB Monday.

Thanks,  
Lisa

*Lisa Kaeser, J.D.  
Director, Office of Legislation and Public Policy  
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**From:** Ott, Sandra (NIH/NICHD) [E]  
**Sent:** Friday, September 13, 2013 12:25 PM  
**To:** Kaeser, Lisa (NIH/NICHD) [E]  
**Cc:** Ott, Sandra (NIH/NICHD) [E]  
**Subject:** WF 324629 - Round 1 Clearance due by COB 09/16/2013  
**Importance:** High

Lisa,

This has been assigned to NICHD, OER, NHLBI, OMA, and OCPL for clearance by COB 09/16/2013. We are to provide our clearance and/or comments (regarding documents named 1 Round 1 Carome and 2 Round 1 SUMMARY STATEMENT) to ES by COB 09/16. The PA on this is Michelle Whitfield.

Sandy

**From:** EDRMS\_NO\_REPLY@mail.nih.gov [mailto:EDRMS\_NO\_REPLY@mail.nih.gov]  
**Sent:** Thursday, September 12, 2013 3:35 PM

**To:** Brown, Crystal (NIH/NICHD) [C]; EDRMS\_NO\_REPLY (NIH/OD); EDRMS\_NO\_REPLY (NIH/OD); Ott, Sandra (NIH/NICHD) [E]; EDRMS\_NO\_REPLY (NIH/OD); Wood, Vandora (NIH/CIT) [C]

**Subject:** WF 324629 - Preview Clearance Status (CC)

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**Work Folder Information**

**Work Folder:** WF 324629

**Process:** IC Clearance WF 324629

**Due Date:** September 16, 2013

**Program Analyst:** Whitfield, Michelle D. (NIH/OD) [E]

**WF Subject:** Public Citizen expresses concern regarding the Transfusion of Prematures (TOP) Trial. Urges the Secretary to stop the study.

**IC:**NICHD

**From:** Carome, Michael; Weaver, Gregory; Wolfe, Sidney;

**To:** Sebelius, Kathleen;

**Remarks:** Assigned to NICHD, OER, NHLBI, OMA, and OCPL for clearance by Sept. 16. Please provide your clearance and/or comments (regarding documents named 1 Round 1 Carome.docx and 2 Round 1 082820131026 SUMMARY STATEMENT Public Citizen TOP 090513 draft.docx) to ES by c.o.b. Sept. 16.

Thank you.

Michael A. Carome, M.D.

Director

Public Citizen's Health Research Group

General Preventive Medicine Resident

1600 20<sup>th</sup> Street, N.W.

Washington, D.C. 20009

Dear Dr. Carome:

Thank you for your letter regarding the Transfusion of Prematures (TOP) Trial. I value your interest in the protection of human subjects. The Office of Human Research Protections (OHRP) is carefully reviewing information related to the TOP trial.

I also appreciate your attendance at the August 28, 2013, public meeting held by the Department of Health and Human Services (HHS). The purpose of the meeting was to seek public input and comment on how certain provisions of the federal policy for the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. OHRP has publicly indicated that the office plans to take no further action on research with this type of study design until the process of producing appropriate guidance is completed. If you have any further questions or concerns, you may contact Dr. Kristine Borrer, Director, Division of Compliance Oversight/OHRP at 240-453-8132.

Thank you again for your interest in this matter. I will also provide this response to the cosigners of your letter.

Sincerely,

Kathleen Sebelius

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]  
**Subject:** RE: WF 324629 - Round 1 Clearance due by COB 09/16/2013  
**Date:** Monday, September 16, 2013 9:10:04 AM  
**Attachments:** AAP\_HHS-OPHS-2013-0004f11.pdf

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I spoke to Lisa – thought (b)(5) the response is really directed for the TOP Trial.

Also – there are a few items of interest from the Public Comment page from the August 28 meeting:

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<http://www.regulations.gov/#!documentDetail;D=HHS-OPHS-2013-0004-0074>

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Happy to discuss further

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(b)(5)

L

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**Process:** IC Clearance WF 324629

**Due Date:** September 16, 2013

**Program Analyst:** Whitfield, Michelle D. (NIH/OD) [E]

**WF Subject:** Public Citizen expresses concern regarding the Transfusion of Prematures (TOP) Trial. Urges the Secretary to stop the study.

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**From:** Carome, Michael;Weaver, Gregory;Wolfe, Sidney;

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**Remarks:** Assigned to NICHD, OER, NHLBI, OMA, and OCPL for clearance by Sept. 16.

Please provide your clearance and/or comments (regarding documents named 1 Round 1 Carome.docx and 2 Round 1 082820131026 SUMMARY STATEMENT Public Citizen TOP 090513 draft.docx) to ES by c.o.b. Sept. 16. Thank you.

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



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September 6, 2013

Jerry Menikoff, M.D., J.D.  
Office for Human Research Protections (OHRP)  
Department of Health and Human Services  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852

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Stuart A. Cohen, MD, MPH, FAAP  
San Diego, CA

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Sara H. Goza, MD, FAAP  
Fayetteville, GA

Dear Dr. Menikoff,

The American Academy of Pediatrics (AAP), a non-profit professional organization of 60,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults appreciates this opportunity to offer comments to the U.S. Department of Health and Human Services (HHS) concerning the public meeting and request for comments on the protection of human subjects in research examining standard of care interventions. These comments have also been endorsed by the American Pediatric Society, the Academic Pediatric Association, the Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research.

The AAP applauds the effort to engage the public and seek input into the protection of human subjects in clinical research. Recent national conversations surrounding the SUPPORT intervention provide a tremendous opportunity to reflect on the critical importance of research to advance clinical care for children and the guidelines and procedures that should be set in place to protect children as a vulnerable group.

Children as a group are underrepresented in clinical research. It is of vital importance that children be permitted to serve as participants in clinical research so that they may gain from both the personal benefits of participation (such as that afforded by access to new treatments only available through clinical trials, or through access to clinical trials that are associated with heightened clinical monitoring that leads to improved clinical outcomes) as well as the benefits that accrue to all children as a group (i.e., so that new treatment options can be developed and evaluated that will benefit children). However, conducting research on children presents unique challenges, including that children are a vulnerable population and they cannot consent for themselves. As such children should receive special protections and consideration in the research approval process as outlined in 45 CFR 46, Subpart D and 21 CFR 50, Subpart D and discussed in the 2004 Institute of Medicine report, "Ethical Conduct of Clinical Research Involving Children."

The AAP understands that the discussion is now broader than the specifics of the

SUPPORT study, however, we wish to highlight several aspects of the study that are important to the larger discussion. First, the oxygen saturation range of 85% to 95% was the standard of practice while the study was being conducted (American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 6<sup>th</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics, 2007). Second, the study investigators and the field of perinatal medicine were operating in a state of scientific uncertainty concerning whether babies receiving oxygen at the high, the low, or the middle range were the most likely to have the best outcomes. The AAP believes that scientific uncertainty is a key element to the ethical conduct of research involving children (Shady, RE, Denne, SC, Committee on Drugs and Committee on Pediatric Research. Clinical report-guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics, 2010, 125(4)850-860). Finally, the SUPPORT study had many other key elements of an ethical study including a scientifically sound protocol, a robust plan to monitor safety during the study, and appropriate expertise to take into consideration the unique physiology of premature babies.

Below we outline I) over-arching ideas the AAP urges HHS to consider in the discussion of human subjects protection for clinical intervention studies and II) specific comments on questions posed about risk assessment for studies examining standard of care interventions.

The AAP urges consideration of the following in the discussion of human subjects protection for clinical research:

- 1) Improving informed consent: The processes of informed consent and pediatric assent are central elements in all clinical research, indispensable for upholding the ethical principle of autonomy and for ensuring the protection of human subjects. In pediatric clinical research, the informed consent process is complemented by the pediatric assent process, and its importance is magnified by the inherent vulnerability of pediatric research subjects. However, best practices for informed consent and pediatric assent processes have never been identified. Currently, there is wide variation in informed consent and pediatric assent practices across the country, and IRBs vary in the criteria they require for approval of informed consent. The complexity of the consent process is highlighted by the fact that 18 IRBs examined the consent form used in the SUPPORT trial and they came to a different conclusion than OHRP concerning what should have been listed as a foreseeable risk. Therefore, the AAP strongly supports the need for additional research to define best practices for both the informed consent and pediatric assent process.
- 2) Representation of trained community members in the research development and approval process: It is important to develop mechanisms to solicit the views of trained community members and parents about how research is evaluated and approved. It is also important to create a system where trained community members and parents can more consistently provide input into specific studies, including the research design and consent procedures during the approval process, especially for difficult or complicated studies. Currently, this happens rarely.

- 3) **Strengthening data and safety monitoring:** Because children are a potentially fragile population, they deserve the highest standards for monitoring safety during a clinical intervention study, especially those investigating new drugs or therapies or interventions with children with complex medical conditions that place them at risk for adverse health outcomes. It is not possible to foresee all risks related to studies in children, and unexpected events can and do occur. Therefore, an independent data safety monitoring committee is necessary for intervention studies seeking to improve clinical care for children. The committee must be comprised of pediatricians and have clear guidelines for early stopping rules. Even for interventions operating within the standard of care with no known risks of participation, a robust data monitoring plan could help determine if unforeseen risks are accruing for children in selected randomized groups, especially in cases where children's clinical condition places them at risk for adverse outcomes.

We offer the following comments for specific questions posed about intervention studies conducted within clinical standards of care:

- 1) *How should an IRB assess risks of standard care interventions provided to subjects in the research context?* Interventions within the standard of care represent best known practices, but these practice standards are not static. Many intervention studies are conducted over multiple years when new information and research findings may emerge. Risk assessment for research on standard of care interventions is an ongoing process that should be informed by careful assessment of existing scientific knowledge and consideration of how different interventions within the standard of care are currently applied in clinical settings. Robust data safety monitoring plans should be in place to detect any unforeseen risks arising in the study. IRB review committees must include pediatric specialists knowledgeable about the special medical, social, and ethical needs of children and standards of risk for clinical interventions with children. Also among the issues of concern here are when standard of care evaluation or revisions become clinical research. Clearer definitions of these boundaries, and when IRB and consent come into play, will help to further good research in this area.
- 2) *What factors should an IRB consider in determining that the research-related risks of standard of care interventions are reasonably foreseeable and therefore required to be disclosed?* Best evidence, generally systematic reviews and/or randomized controlled trials if available. Levels of evidence are expected to be included with protocol submissions. It is essential that pediatricians and child health professionals with clinical expertise in the areas under investigation review protocols so that standard of care and research risks can be appropriately assessed for children.

- 3) *How should randomization be considered in research studying interventions within the standard of care?* Assuming true uncertainty about the risks and benefits of participation in different treatments, randomization to interventions that are within the standard of care should not be considered to present heightened risk to subjects.
- 4) *Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions?* Obtaining the informed consent of research subjects prior to their participation is regarded as a cornerstone for the ethical conduct of research, and a fundamental protection for participants' rights. Research involving randomization to one or more standard of care interventions should follow the same requirements for informed consent as other research studies and should not be assumed to involve no more than minimal risk.

The AAP appreciates the opportunity to offer commentary concerning the protection of human subjects in clinical intervention studies and stands ready to assist HHS in considering the unique issues related to children's involvement in medical research.

Sincerely,



Thomas K. McInerney, MD, FAAP  
President

TM: kl, lo

**From:** Luc Brion  
**To:** Mcbrien, James, D  
**Cc:** Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Manuscript Entitled "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" \*Sent on Behalf of William E. Truog, MD\*  
**Date:** Sunday, September 15, 2013 5:46:43 PM  
**Attachments:** Review on pCO2 in SUPPORT.docx

---

Jim:

Thank you for the privilege of reviewing this manuscript

Here are my comments.

Best regards,

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal  
Medicine  
The University of Texas Southwestern Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-9063

Office: (214) 648-3903

Fax: (214) 648-2481

luc.brion@utsouthwestern.edu

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---

**From:** Mcbrien, James, D [mailto:jdmcbrien@cmh.edu]

**Sent:** Friday, September 06, 2013 2:42 PM

**To:** Luc Brion

**Cc:** Truog, William (MD); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** Manuscript Entitled "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" \*Sent on Behalf of William E. Truog, MD\*

Dear Dr. Brion,

The enclosed manuscript entitled "Association of PaCO2 with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)" is being sent for internal Neonatal Network Research review. Would you be able to review the manuscript by **September 20, 2013**? There are no particular guidelines for the review except to look at study

design, validity, clarity of results, and appropriateness of interpretation.

Thanks,

Jim

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Sunday, September 15, 2013

From: Luc P Brion, MD

To: McBrien, James, D

"Association of paco<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)"

Thank you for asking me to review this manuscript.

The authors assessed the association of pCO<sub>2</sub> values during the first 2 weeks of life with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD) and neurodevelopmental impairment (NDI) in 1316 infants enrolled in the SUPPORT trial.

They found that higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment. A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if median SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> & ventilator days, supporting higher Max PaCO<sub>2</sub> as a marker of illness severity.

The manuscript is well written, with strong background, design and methods. Interpretation and conclusions match the results well.

Page 4, last paragraph: The statement "(a PaCO<sub>2</sub>>65 mm Hg permitted intubation, while a PaCO<sub>2</sub><65 mm Hg with a pH>7.20 was a mandatory extubation criterion)" seems impossible to achieve. I would also mention other SUPPORT criteria for extubation, i.e., sPO<sub>2</sub> >88% with FiO<sub>2</sub> < 0.5, mean airway pressure <10, ventilator rate <20, absence of clinically significant PDA, and amplitude < 2x mean airway pressure for patients on HFO.

Page 5: Hypotheses: I would suggest explaining the reason justifying each hypothesis and state whether each hypothesis addresses actual or target saturation or both. My reading is that you hypothesized that hypercapnia would only be associated with sIVH in patients with the low saturation target; I cannot find in the background why you selected this hypothesis. It is not clear whether hypothesis of interaction with BPD was with SPO<sub>2</sub> target or group; background page 4 supports using SPO<sub>2</sub> target for this interaction. Could low pCO<sub>2</sub> (associated with IVH and with PVL) also be associated with higher risk of NDI?

Page 7: I would suggest considering an additional analysis of pCO<sub>2</sub>, separating different postnatal ages, e.g., up to 4 days and 5-14 days. Previous studies have shown an association during the first 3-4 days (Fabres, Kaiser). The current study shows that the analysis is significant when using the first 14 days; however, it does not show whether this remain significant after the first week of life, i.e., after most

severe IVHs have already taken place. The relationship between pCO<sub>2</sub> and BPD may behave differently and remain significant for 14 days.

Page 8, paragraph 1: was interaction with actual median sPO<sub>2</sub> tested for maximum pCO<sub>2</sub>, which on bivariate analysis has the highest difference?

Results page 8: This paragraph is difficult to follow because it starts with PCO<sub>2</sub> effects, goes to sPO<sub>2</sub> effects and back to pCO<sub>2</sub> effects. No information is provided on interaction of maximum pCO<sub>2</sub> and SPO<sub>2</sub>; the first statement about lack of interaction is on page 11 in the discussion. I would reorganize the paragraph one of 2 ways: either in 3 sections, describing each the result for PCO<sub>2</sub> and the interaction with SPO<sub>2</sub>; or in 2 sections, first describing results with pCO<sub>2</sub> and then interaction with sPO<sub>2</sub>.

Page 9: BPD/death: What was the frequency of airleak among fluctuators?

Page 9: NDI/death and death: was sIVH tested as one possible variable associated with NDI/death?

Page 10: I would move the first 6 lines (up to "calculated") to the methods section. I would replace "correlations" by "relationship" on line 4; correlation was not used for severe illness. Was maximum FiO<sub>2</sub> obtained at the same time as max pCO<sub>2</sub> or any time during the first 14 days, excluding delivery room (and admission to the NICU before optimizing mean airway pressure?)? Since FiO<sub>2</sub> depends on mean airway pressure, you may consider also analyzing the relationship between max pCO<sub>2</sub> and maximum respiratory severity score (mean airway pressure x FiO<sub>2</sub>) (Merrill, Journal of Perinatology (2011) 31, 599-606).

Discussion: Page 11: I would add death to the first sentence: "Extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI)."

Page 11 second paragraph: "No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups,..." This sentence applies only to sIVH. It address the difference between the hypothesis for sIVH (interaction with saturation target) and what was observed (interaction with saturation group) and may be more useful in paragraph 2 of page 12.

Page 13, end of first paragraph: Can volutrauma/atelectrauma be assumed in all patients with fluctuating pCO<sub>2</sub> (e.g., those on SIMV and volume-targeted ventilation adjusted for loops)? Could other factors be relevant, e.g., air leak (please see above), inflammation, respiratory drive? You may want to discuss the role of FiO<sub>2</sub> in lung injury.

Tables: Tables 1-4 are hard to understand at first reading. I would suggest using 4 columns; this would show pCO<sub>2</sub> variable in the first column and subgroups in the second column.

Table 1: It is difficult to understand where sPO<sub>2</sub> 91 and 94 came from; it may be easier to understand if all values were shown in the table rather than in the text (91,92,93,94). I would replace SPO<sub>2</sub> with actual SPO<sub>2</sub> target

Table 2: I would replace SPO<sub>2</sub> with SPO<sub>2</sub> target

**Supplemental Table 4: antenatal steroids; these numbers appear incorrect; they likely represent those exposed to NO antenatal steroids rather than those who received antenatal steroids.**

**From:** Luc Brion  
**To:** Roy Heyne; "doctorlevan@gmail.com"; "Wrage, Lisa Ann"; "Barbara Stoll"; "nfiner@ucsd.edu"; "Wally Carlo, M.D."; "Gantz, Marie"; Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Gantz, Marie"; Mambarambath Jaleel; Myra Wyckoff; "Pablo.Sanchez@nationwidechildrens.org"  
**Subject:** FW: Submission Confirmation for Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial  
**Date:** Friday, September 13, 2013 3:52:11 PM

---

I submitted the manuscript to Journal of Pediatrics.  
Thanks for your collaboration.  
Let's hope for the best and best regards,  
Luc

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

From: ees.jpeds.0.23e348.b2a679c1@eesmail.elsevier.com  
[mailto:ees.jpeds.0.23e348.b2a679c1@eesmail.elsevier.com] On Behalf Of Journal Office  
Sent: Friday, September 13, 2013 2:49 PM  
To: Luc Brion; lucbrion@gmail.com  
Subject: Submission Confirmation for Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Dear Dr. Brion,

Your submission entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" has been received by The Journal of Pediatrics. If you did not include a list of 5-7 possible reviewers in your Letter of Submission, please reply to this e-mail with a list of 5-7 appropriate reviewers for your submission (not needed for Letters to the Editor, Insights and Images, or Editorials submissions); be sure to provide contact information--the e-mail address, at minimum--of the suggested reviewers. Potential reviewers must be outside of the authors' institution(s), with no known potential conflicts of interest. Not providing 5-7 potential reviewers may result in delays in the processing of your manuscript.

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- \* A statement of any potential conflict of interest, real or perceived; this includes a description of the role of the study sponsor(s), if any, in: (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication. Include statements even when the sponsor had no involvement in the above matters. This information must also appear on the title page of the manuscript. Additional information is available at <http://jpeds.com/authorinfo#conf>;
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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 12, 2013 9:27 AM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Muy bien. Hasta entonces.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 12, 2013 9:26 AM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Yes, we do.

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 12, 2013 8:49 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Renate, does John's office have a wireless Internet connection like Building 31 does? I'd like to bring my laptop, just in case we need to access a file in a hurry.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 5:38 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

I can come over  
1030 is fine

I sent bob some talking points. I can come over earlier to go over what I will say

Sent from my iPhone

On Sep 11, 2013, at 5:30 PM, "Myles, Renate (NIH/OD) [E]" <[mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)> wrote:

Hi Rose and Bob:

Can you do 10:30 a.m. for 20 minutes? Also, I'm just realizing Rose is on Executive Blvd. (not 31 like I thought). Any chance you and Bob could come to Bldg. 1?

Renate

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 4:13 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

One more thing – I am flying to (b)(6) and plan on leaving work around 12 noon.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 4:01 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Heads up! I thought (b)(5) How about I send the (b)(5)

(b)(5) Rose: would you be (b)(5)

(b)(5)

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 3:47 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

This is fine but why (b)(5)

Kathy Hudson, Ph.D.  
Deputy Director for Science, Outreach, and Policy  
NIH  
301 496 1455  
[kathy.hudson@nih.gov](mailto:kathy.hudson@nih.gov)

On Sep 11, 2013, at 3:33 PM, "Myles, Renate (NIH/OD) [E]" <[mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)> wrote:

Hi Kathy and Steph:

CBS is coming back with more questions. The producer asked if someone would be willing to talk to her about the surfactant issue but we have a written response to her questions. Please let me know if you have any concerns with these responses.

Thanks,  
Renate

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**When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.**

(b)(5)

**On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).**

(b)(5)

---

**From:** Devaney, Stephanie (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 7:04 PM  
**To:** Myles, Renate (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Renate -  
Can you change the 2nd sentence to:

(b)(5)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 06:19 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

I'm getting pinged by the producer on this; are you okay with the revision below?

Thanks,  
Renate

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 1:09 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

See clarifying points highlighted in yellow below to your note in red. Let me know if this looks okay.

Thanks,  
Renate

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 10:59 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

See note in red.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 4:57 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

Kim Skeen of CBS had some additional follow up questions. The proposed answers are included below for your review (NICHD has reviewed it).

ADD

Kim Skeen had additional questions:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

(b)(5)

(b)(5)

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

(b)(5)

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

(b)(5)

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 9:31 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

This is fine renate. Thank you

Kathy Hudson, Ph.D.  
Deputy Director for Science, Outreach, and Policy  
NIH  
301 496 1455  
[kathy.hudson@nih.gov](mailto:kathy.hudson@nih.gov)

On Sep 5, 2013, at 5:04 PM, "Myles, Renate (NIH/OD) [E]" <[mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)> wrote:

Note update on participants. We're linking to the NEJM article since those reflect the participants at the time.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 4:43 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** TIME SENSITIVE FOR REVIEW: SUPPORT Study  
**Importance:** High

Hi Kathy:

Kim Skeen of CBS Sunday Morning had some follow up questions from her interview at the SUPPORT public meeting. The answers below were

**vetted by NICHD experts. Can you take a quick look and let me know if you have any concerns before I send to HHS for clearance?**

ADD

Kim Skeen  
CBS Sunday Morning

Kim had follow up questions. NIH responses are below:

- 1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

(b)(5)

- 2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

- 3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study  
**Date:** Thursday, September 12, 2013 9:18:39 AM

---

1030 am this morning - going to Building 1 shortly

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

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

**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Thursday, September 12, 2013 9:09 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Are you done with CBS are waiting to talk to them?  
Best wishes.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human  
Development National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
rajut@mail.nih.gov

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 5:40 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** Fwd: TIME SENSITIVE FOR REVIEW: SUPPORT Study

FYI  
Budding 1 has decided I can talk to CBS May be a little late for BM

Sent from my iPhone

Begin forwarded message:

**From:** "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov>  
**Date:** September 11, 2013, 5:30:41 PM EDT  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

Cc: "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov>  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Rose and Bob:

Can you do 10:30 a.m. for 20 minutes? Also, I'm just realizing Rose is on Executive Blvd. (not 31 like I thought). Any chance you and Bob could come to Bldg. 1?

Renate

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, September 11, 2013 4:13 PM  
To: Myles, Renate (NIH/OD) [E]  
Cc: Bock, Robert (NIH/NICHD) [E]  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

One more thing – I am flying to (b)(6) and plan on leaving work around 12 noon.

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

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higginsr@mail.nih.gov

From: Myles, Renate (NIH/OD) [E]  
Sent: Wednesday, September 11, 2013 4:01 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Bock, Robert (NIH/NICHD) [E]  
Subject: FW: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Heads up! I thought (b)(5) How about I send the (b)(5)  
(b)(5) Rose: would you be (b)(5)  
(b)(5)

From: Hudson, Kathy (NIH/OD) [E]  
Sent: Wednesday, September 11, 2013 3:47 PM  
To: Myles, Renate (NIH/OD) [E]  
Cc: Devaney, Stephanie (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
Subject: Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

This is fine but why (b)(5)

Kathy Hudson, Ph.D.

Deputy Director for Science, Outreach, and Policy

NIH

301 496 1455

kathy.hudson@nih.gov

On Sep 11, 2013, at 3:33 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Hi Kathy and Steph:

CBS is coming back with more questions. The producer asked if someone would be willing to talk to her about the surfactant issue but we have a written response to her questions. Please let me know if you have any concerns with these responses.

Thanks,

Renate

When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT

study. If this is NOT correct, please let us know.

(b)(5)

On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).

(b)(5)

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Sent: Monday, September 09, 2013 7:04 PM  
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Cc: Burklow, John (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
Subject: Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Renate -  
Can you change the 2nd sentence to:

(b)(5)

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Cc: Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E];  
Abel, Kathy (NIH/OD) [E]  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

I'm getting pinged by the producer on this; are you okay with the revision below?

Thanks,

Renate

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Cc: Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E];  
Abel, Kathy (NIH/OD) [E]  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

See clarifying points highlighted in yellow below to your note in red. Let me know if this looks okay.

Thanks,

Renate

From: Hudson, Kathy (NIH/OD) [E]  
Sent: Monday, September 09, 2013 10:59 AM  
To: Myles, Renate (NIH/OD) [E]  
Cc: Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E];  
Abel, Kathy (NIH/OD) [E]  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

See note in red.

From: Myles, Renate (NIH/OD) [E]  
Sent: Friday, September 06, 2013 4:57 PM  
To: Hudson, Kathy (NIH/OD) [E]  
Cc: Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E];  
Abel, Kathy (NIH/OD) [E]  
Subject: RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

Kim Skeen of CBS had some additional follow up questions. The proposed answers are included below for your review (NICHD has reviewed it).

ADD

Kim Skeen had additional questions:

We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?

(b)(5)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]  
Sent: Thursday, September 05, 2013 9:31 PM  
To: Myles, Renate (NIH/OD) [E]  
Cc: Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E];  
Abel, Kathy (NIH/OD) [E]  
Subject: Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

This is fine renate. Thank you

Kathy Hudson, Ph.D.

Deputy Director for Science, Outreach, and Policy

NIH

301 496 1455

kathy.hudson@nih.gov

On Sep 5, 2013, at 5:04 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Note update on participants. We're linking to the NEJM article since those reflect the participants at the time.

From: Myles, Renate (NIH/OD) [E]  
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Abel, Kathy (NIH/OD) [E]  
Subject: TIME SENSITIVE FOR REVIEW: SUPPORT Study  
Importance: High

Hi Kathy:

Kim Skeen of CBS Sunday Morning had some follow up questions from her interview at the SUPPORT public meeting. The answers below were vetted by NICHD experts. Can you take a quick look and let me know if you have any concerns before I send to HHS for clearance?

ADD

Kim Skeen

CBS Sunday Morning

Kim had follow up questions. NIH responses are below:

1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.

(b)(5)

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time: <http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

(b)(5)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 7:53 PM  
**To:** Howse, Jennifer  
**Cc:** Hudson, Kathy (NIH/OD) [E]  
**Subject:** Re: SUPPORT

We look forward to it.

Thanks, Alan

Alan E. Guttmacher, M.D.  
Director  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health

On Sep 11, 2013, at 7:50 PM, "Howse, Jennifer" <[JHowse@marchofdimes.com](mailto:JHowse@marchofdimes.com)> wrote:

Alan and Kathy- Thanks for sending along the materials I requested to better inform my team . Following our internal discussions around issues surrounding the SUPPORT trial, I will set up time for us to continue our dialogue.

With best regards,  
Jennifer

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:22 PM  
**To:** Howse, Jennifer  
**Cc:** Hudson, Kathy (NIH/OD) [E]  
**Subject:** SUPPORT

Jennifer –

Thanks for taking the time to talk last week about the SUPPORT trial. We wanted to send you background materials, as promised. Attached are:

1. NEJM perspective written by Francis and both of us, "In Support of SUPPORT — A View from the NIH"
2. OHRP letters to UAB
  - a. March 7, 2013
  - b. June 4, 2013
3. Public Citizen letters to the Secretary
  - a. SUPPORT Study – April 10, 2013
  - b. TOP Trial – August 22, 2013
4. A letter to NEJM from ~40 bioethicists.

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5. **Not attached, but worth reading, is John Lantos' essay:**

<http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blogid=140>

Let's touch base again whenever makes sense to you. Thanks again for your thoughtful consideration of this.

Alan and Kathy

**Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 6:08 PM  
**To:** NIH NMB (NIH/OD)  
**Subject:** Accepted: CBS News background interview with Rose Higgins on SUPPORT Study

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 5:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Yes, good idea and I'll fill John in on some of the background you provided. He's coming out of meetings at 10 which may run over so why don't we plan to meet at 10:15 a.m. in John's office 1/344.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 5:38 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

I can come over  
1030 is fine

I sent bob some talking points. I can come over earlier to go over what I will say

Sent from my iPhone

On Sep 11, 2013, at 5:30 PM, "Myles, Renate (NIH/OD) [E]" <[mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)> wrote:

Hi Rose and Bob:

Can you do 10:30 a.m. for 20 minutes? Also, I'm just realizing Rose is on Executive Blvd. (not 31 like I thought). Any chance you and Bob could come to Bldg. 1?

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Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**Subject:** Re: TIME SENSITIVE FOR REVIEW: SUPPORT Study

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Kathy Hudson, Ph.D.  
Deputy Director for Science, Outreach, and Policy  
NIH  
301 496 1455  
[kathy.hudson@nih.gov](mailto:kathy.hudson@nih.gov)

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**On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few**

**background questions including why the brand/type of surfactant used would not possibly affect the results).**

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Hi Kathy:

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Hi Kathy:

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Kim Skeen  
CBS Sunday Morning

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1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we**

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT Study 4 11 13  
**Date:** Wednesday, September 11, 2013 4:29:18 PM  
**Attachments:** [SUPPORT Study 4 11 13.docx](#)

---

I found the original SUPPORT talking points – we could work from these (changing the OHRP items based on the June 6 NEJM publication).

Thanks  
Rose

## SUPPORT Study

- The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT), co-funded by the National Institute on Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI), study sought to evaluate the standard of care for administering oxygen to very preterm infants, born at 24 to 27 weeks gestation.
- **The standard of care at the time of the trial for administering oxygen to preterm infants was an oxygen saturation range of 85 to 95 percent. This standard comes from the guidelines issued by the American Academy of Pediatrics.**
- **One arm of the study aimed to determine if the lower range (85-89 percent) or higher (90-95 percent) range of oxygen saturation within this standard of care was more effective for improving the outcome for preterm babies.**
- **It is critical to note that this treatment or the rationale of the study has never been in question by the Office for Human Research Protections (OHRP).**
- The infants in the study had a lower mortality rate than those not enrolled. When adjusted for characteristics of the non-enrolled infants, such as poorer health, the children in the study were still at no greater risk of death.

### Percent Mortality:

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

- While language about the potential risks of the standard of care was included in the consent form, the OHRP cited the study for not describing the risks of the oxygen saturation arm as clearly as possible. Specifically, OHRP cited the study for not clearly stating the risks associated with being in the higher or the lower range of the standard of care.
  - The consent forms did include language in the section describing immediate care practices that infants enrolled in the study would be at risk “during resuscitation after birth, including the need for chest compressions, rescue medications, and even death.”
- **The NIH values the insights of the OHRP and will work to ensure that all potential risks in all Neonatal Research Network (NRN) study consent forms are clearly described in all appropriate parts of the forms.**
- **Now in addition to the Institutional Review Boards (IRB) at the individual institutions, the Pregnancy and Perinatology Branch maintains copies of the individual IRB approved consent forms for each NRN study. In addition, a Data Safety and Monitoring Committee now reviews the consent forms before the start of all Neonatal Research Network studies.**

### SUPPORT Study Findings:

- Higher oxygen levels improved preterm infants’ survival but increased the risk of retinopathy of prematurity.
- Continuous positive airway pressure (CPAP) was as effective as the traditional ventilator/surfactant therapy in treating BPD in these infants, but CPAP may result in fewer complications.
- Follow-up results at 18 to 22 months’ corrected age showed no significant difference in death or neurodevelopmental impairment between infants who received CPAP and those who received surfactant/intubation, and no difference between those who received lower and higher oxygen levels.
- Infants recruited into a neuroimaging secondary study examining early head ultrasound and MRI findings compared with neurodevelopmental outcomes at 18 to 22 months are currently being followed up at between 6 and 7 years of age to see how well the initial MRIs predict outcomes at school age.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Myles, Renate \(NIH/OD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Wednesday, September 11, 2013 2:55:45 PM

---

I checked and this is good to go

Thanks for your patience

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 2:43 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: CBS News questions regarding RTI

Sure thing.

Sent from my BlackBerry 10 smartphone.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:31 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate, can you hold off for a few minutes? Rose wants to check something.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:26 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Sure

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch

NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:25 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

(b)(5)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:25 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:21 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Please see attached. Is there another phrase we could use, rather than (b)(5) study?"

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:15 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I've reconciled the drafts and will send shortly.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 2:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks, Rose. Can you tweak the language where you think it needs tweaking?

Also, you (b)(5)

(b)(5)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:59 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate – CBS seems to be focusing on surfactant – it is really a management strategy on which the study was developed.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 1:54 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I've made some comments and points in the attached for your consideration.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:46 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

A couple of minor points

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:37 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Please see attached.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 12:00 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 11, 2013 11:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

We would prefer to do a quick call if possible—would 2 PM today work? It doesn't have to be a conference call involving a lot of staff—just one person talking to Sharyl for some background would be fine. We know we have taken up a lot of your time and we really appreciate your patience with us! Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
410-591-9567 cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Wednesday, September 11, 2013 8:05 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Yes, your statement is correct.

I will check to see if we can get someone to speak to Sharyl on background to explain surfactants but for expediency's sake, it would probably be easier to get answers to her question via email since our folks are so busy. Could you send them along? In the meantime, I am going to try and line up a call.

Best,  
Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Tuesday, September 10, 2013 8:10 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate,

When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.

On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).

I will be at my desk Wednesday morning if you would like to give me a call. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Monday, September 09, 2013 9:24 PM  
**To:** Skeen, Kim

**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Apologies, again, for the delay; following are responses to your questions attributable to NIH generally:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

There were 25 IRBs overseeing the institutions in the Neonatal Research Network at the time the SUPPORT Study was undertaken, including the one at the Data Coordinating Center (RTI); however, the Data Coordinating Center did not see patients and so it did not produce a consent form for the study and its IRB did not review one. Therefore, it is accurate to say that IRBs for each of the institutions taking part in the study (24 in all) each reviewed consent forms for the institutions they served.

The Data Coordinating Center did have its IRB review its role in coordinating the SUPPORT study data. But as noted above, the Data Coordinating Center's IRB did not review or approve a patient consent form for the SUPPORT study because the Center's role is to coordinate data, not to see patients.

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

Results data associated with various published studies on the SUPPORT trial are publicly available in the journals in which the studies were published. Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites.

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

There are several surfactants available in the U.S. and the type of surfactant was determined by the individual sites and not dictated by the protocol. Information on which surfactant formulation a site used may be available from that site. It may help you to know that in its letter to the University of Alabama last March, OHRP noted that it was not concerned with the arm of the study comparing surfactant treatment to CPAP.

Best,  
Renate

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

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Monday, September 09, 2013 6:19 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Renate,

We are still looking for answers to the questions we submitted last week (see below). Please provide a response.

- What is the correct number of IRB's for the SUPPORT study? We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Thank you.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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

From: Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]

Sent: Friday, September 06, 2013 12:36 PM

To: Skeen, Kim

Subject: Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

From: Skeen, Kim

Sent: Friday, September 6, 2013 12:27 PM

To: Myles, Renate (NIH/OD) [E]

Subject: RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<mailto:skeenk@cbsnews.com>

From: Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]

Sent: Friday, September 06, 2013 11:17 AM

To: Skeen, Kim

Subject: RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,

Renate

From: Skeen, Kim [<mailto:SkeenK@chsnews.com>]

Sent: Friday, September 06, 2013 10:57 AM

To: Myles, Renate (NIH/OD) [E]

Subject: FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?

o We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).

o Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:

<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,

Renate

Renate Myles, MBA

Acting Chief

News Media Branch

National Institutes of Health

Tel: 301-435-3638

Email: [mylesr@mail.nih.gov](mailto:mylesr@mail.nih.gov)<<mailto:mylesr@mail.nih.gov>>

Web: <http://www.nih.gov><<http://www.nih.gov>>

NIH . . . Turning Discovery Into Health

Celebration of Science at NIH<<http://www.youtube.com/watch?v=gYkP9ED5naA>>: watch how medical research saves lives and improves health

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]

**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

**Sent:** Thursday, September 05, 2013 11:33 AM

**To:** Skeen, Kim

**Cc:** Spangenberg, Kami

**Subject:** RE: CBS News is trying to reach you

Kim,

Sorry for the delay.

NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.

RTI's NIH funding information is publicly available from NIH.

The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]

Sent: Thursday, September 05, 2013 11:23 AM

To: Bistreich-Wolfe, Lisa

Subject: RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

**From:** Skeen, Kim

**Sent:** Wednesday, September 04, 2013 3:09 PM

**To:** 'Bistreich-Wolfe, Lisa'

**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

**Sent:** Wednesday, September 04, 2013 3:02 PM

**To:** Skeen, Kim

**Cc:** Spangenberg, Kami

**Subject:** RE: CBS News is trying to reach you

Kim,

RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]

Sent: Wednesday, September 04, 2013 11:53 AM

To: Bistreich-Wolfe, Lisa

Subject: RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

410-591-9567 cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

Sent: Wednesday, September 04, 2013 11:24 AM

To: Skeen, Kim

Cc: Spangenberg, Kami

Subject: RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

#### RTI International's Role in the NICHD Neonatal Network SUPPORT Study

We are aware of concerns voiced about the informed consent document regarding this particular study.

RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.

As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,

Lisa

Lisa Bistreich-Wolfe

Media Relations Manager

RTI International

919.316.3596

[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

From: Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]

Sent: Tuesday, September 03, 2013 4:55:51 PM

To: News

Subject: CBS News is trying to reach you Auto forwarded by a Rule

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:21 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI  
**Attachments:** 3 Draft response skeen.docx

Please see attached. Is there another phrase we could use, rather than (b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 2:15 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I've reconciled the drafts and will send shortly.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 2:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks, Rose. Can you tweak the language where you think it needs tweaking?

Also, you (b)(5)

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:59 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate – CBS seems to be focusing on surfactant – it is really a management strategy on which the study was developed.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 1:54 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I've made some comments and points in the attached for your consideration.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:46 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

A couple of minor points

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 1:37 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Please see attached.

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 12:00 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 11, 2013 11:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

We would prefer to do a quick call if possible—would 2 PM today work? It doesn't have to be a conference call involving a lot of staff—just one person talking to Sharyl for some background would be fine. We know we have taken up a lot of your time and we really appreciate your patience with us! Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau

202-457-4383 office  
410-591-9567 cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Wednesday, September 11, 2013 8:05 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Yes, your statement is correct.

I will check to see if we can get someone to speak to Sharyl on background to explain surfactants but for expediency's sake, it would probably be easier to get answers to her question via email since our folks are so busy. Could you send them along? In the meantime, I am going to try and line up a call.

Best,  
Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Tuesday, September 10, 2013 8:10 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate,

When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.

On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).

I will be at my desk Wednesday morning if you would like to give me a call. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Monday, September 09, 2013 9:24 PM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Apologies, again, for the delay; following are responses to your questions attributable to NIH generally:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

There were 25 IRBs overseeing the institutions in the Neonatal Research Network at the time the SUPPORT Study was undertaken, including the one at the Data Coordinating Center (RTI); however, the Data Coordinating Center did not see patients and so it did not produce a consent form for the study and its IRB did not review one. Therefore, it is accurate to say that IRBs for each of the institutions taking part in the study (24 in all) each reviewed consent forms for the institutions they served.

The Data Coordinating Center did have its IRB review its role in coordinating the SUPPORT study data. But as noted above, the Data Coordinating Center's IRB did not review or approve a patient consent form for the SUPPORT study because the Center's role is to coordinate data, not to see patients.

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

Results data associated with various published studies on the SUPPORT trial are publicly available in the journals in which the studies were published. Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites.

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

There are several surfactants available in the U.S. and the type of surfactant was determined by the individual sites and not dictated by the protocol. Information on which surfactant formulation a site used may be available from that site. It may help you to know that in its letter to the University of Alabama last March, OHRP noted that it was not concerned with the arm of the study comparing surfactant treatment to CPAP.

Best,  
Renate

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

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Monday, September 09, 2013 6:19 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Renate,

We are still looking for answers to the questions we submitted last week (see below). Please provide a response.

- What is the correct number of IRB's for the SUPPORT study? We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?

- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com

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

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]  
Sent: Friday, September 06, 2013 12:36 PM  
To: Skeen, Kim  
Subject: Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

From: Skeen, Kim  
Sent: Friday, September 6, 2013 12:27 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]  
Sent: Friday, September 06, 2013 11:17 AM  
To: Skeen, Kim  
Subject: RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Friday, September 06, 2013 10:57 AM  
To: Myles, Renate (NIH/OD) [E]  
Subject: FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?

We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).

Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)

With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:

<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

Renate Myles, MBA  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [mylesr@mail.nih.gov](mailto:mylesr@mail.nih.gov)<<mailto:mylesr@mail.nih.gov>>  
Web: <http://www.nih.gov><<http://www.nih.gov/>>

NIH . . . Turning Discovery Into Health

Celebration of Science at NIH<<http://www.youtube.com/watch?v=gYkP9ED5naA>>: watch how medical research saves lives and improves health

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Thursday, September 05, 2013 12:39 PM  
To: Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
Cc: Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
Subject: CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and,

more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Thursday, September 05, 2013 11:33 AM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

• NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.

• RTI's NIH funding information is publicly available from NIH.

• The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

From: Skeen, Kim [mailto:Skeenk@cbsnews.com]  
Sent: Thursday, September 05, 2013 11:23 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Skeen, Kim  
Sent: Wednesday, September 04, 2013 3:09 PM  
To: 'Bistreich-Wolfe, Lisa'  
Subject: RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Wednesday, September 04, 2013 3:02 PM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

From: Skeen, Kim [mailto:Skeenk@cbsnews.com]  
Sent: Wednesday, September 04, 2013 11:53 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Wednesday, September 04, 2013 11:24 AM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

We are aware of concerns voiced about the informed consent document regarding this particular study.

RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.

As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
www.rti.org/newsroom

-----  
From: Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
Sent: Tuesday, September 03, 2013 4:55:51 PM  
To: News  
Subject: CBS News is trying to reach you Auto forwarded by a Rule

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

**When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.**

We can definitively tell you that the patient-level data has not been shared outside the network. There was no funding support provided by any corporate entity for the study.

**On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).**

There are several formulations of surfactant on the market that have been approved by the U.S. Food and Drug Administration for treating respiratory distress syndrome. All of the surfactants used in the study were in widespread use in the United States, with no evidence that any one was more effective than the other. The study was designed as a management strategy study—to compare surfactant therapy to CPAP therapy—not to compare the effectiveness of surfactants. Therefore, the type of surfactant was not specified in the study design and any FDA-approved surfactant could be used.

Additional information on the study is available from the 2010 news release describing the study results, at <https://www.nichd.nih.gov/news/releases/Pages/051610-preterm-survival.aspx>.

**From:** Luc Brion  
**To:** Roy Heyne; "doctorlevan@gmail.com"; "Wrage, Lisa Ann"; "Barbara Stoll"; "nfiner@ucsd.edu"; "Wally Carlo, M.D."; "Gantz, Marie"; Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Gantz, Marie"; Mambarambath Jaleel; Myra Wyckoff; "Pablo.Sanchez@nationwidechildrens.org"  
**Subject:** RE: Updated manuscript on changes after SUPPORT for Journal of Pediatrics  
**Date:** Wednesday, September 11, 2013 2:11:20 PM  
**Attachments:** Letter of submission 090913.docx  
Jackie LeVan Manuscript NRN 09-11-13 rev.docx

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Here is the revised latest version.

Please let me know if there is any additional change.

Unless I receive any additional comments I will submit this manuscript to Journal of Pediatrics on Friday 9/13/13.

Thanks for your collaboration.

Best regards,

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The  
University of Texas Southwestern Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-9063  
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[luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)

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---

**From:** Roy Heyne  
**Sent:** Wednesday, September 11, 2013 12:59 PM  
**To:** Luc Brion; 'doctorlevan@gmail.com'; 'Wrage, Lisa Ann'; 'Barbara Stoll'; 'nfiner@ucsd.edu'; 'Wally Carlo, M.D.'; 'Gantz, Marie'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Gantz, Marie'; Mambarambath Jaleel; Myra Wyckoff; 'Pablo.Sanchez@nationwidechildrens.org'  
**Subject:** RE: Updated manuscript on changes after SUPPORT for Journal of Pediatrics

Letter of submission looks fine except in last sentence, need to change "Pediatrics" to "Journal of Pediatrics."

You've addressed all my comments/edits in the manuscript. Combined Table 2 looks good. Other changes look fine as well. One minor that I happened to notice in References is that there is an extra comma in Ref 19 between Barbara Stoll's last name and her initials.

---

**From:** Luc Brion

**Sent:** Monday, September 09, 2013 5:09 PM

**To:** 'doctorlevan@gmail.com'; 'Wrage, Lisa Ann'; 'Barbara Stoll'; 'nfiner@ucsd.edu'; 'Wally Carlo, M.D.'; Roy Heyne; 'Gantz, Marie'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Das, Abhik'; 'Gantz, Marie'; Mambarambath Jaleel; Myra Wyckoff; 'Pablo.Sanchez@nationwidechildrens.org'

**Subject:** Updated manuscript on changes after SUPPORT for Journal of Pediatrics

Roy, Lisa, Jackie et al:

Thanks for all the comments and suggestions.

I made several additional changes to fit requirements for Journal of Pediatrics.

I attach for your review a revised version manuscript for J Peds (one with edits and one clean version) and the letter of submission.

Best regards,

Luc

---

UT Southwestern Medical Center  
The future of medicine, today.



Department of Pediatrics  
Division of Neonatal-Perinatal Medicine

Monday, September 09, 2013

William F. Balistreri, MD  
The Journal of Pediatrics  
Cincinnati Children's Hospital Medical Center  
3333 Burnet Ave, MLC 3021  
Cincinnati, OH 45229-3039

Dear Dr. Balistreri:

We would like to submit an original manuscript entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" for publication in *Journal of Pediatrics*.

We have previously submitted to *Pediatrics* a related manuscript, which was just accepted for publication. In that manuscript, entitled "Change in Process of Care Among Non-Enrolled Patients During and After a Randomized Trial" we had assessed changes in delivery room intubation at Parkland Memorial Hospital during SUPPORT and before publication of SUPPORT in comparison to a period before SUPPORT (January 2003-June 2005). This manuscript is described in the discussion of current manuscript (reference 21). The current manuscript assesses changes in clinical practice and outcome in the NICHD Neonatal Research Network after publication of the SUPPORT Trial in comparison with those before SUPPORT. Parkland Memorial Hospital was part of the NICHD Network during the period of the study. Therefore, data from patients born at Parkland Memorial Hospital before SUPPORT (1/1/2003-12/31/2004) are included along with those in 10 other NICHD Neonatal Research Network centers in the current manuscript. Since data from patients born at Parkland Memorial Hospital before SUPPORT (1/1/2003-12/31/2004) are included in both manuscripts, we have uploaded the proof of the manuscript in press in *Pediatrics* along with the current submission.

The manuscript has not been and will not be submitted to any other journal while it is under consideration by *The Journal of Pediatrics*.

There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Dr. Jaclyn LeVan wrote the first draft of the manuscript.

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Contributions of each authors are provided below:

Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr. Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Here is a list of potential reviewers:

Jack Sinclair, MD: 1200 Main Street West, Hamilton, Ontario, Canada, Fax 905.521.5007, [sinclair@mcmaster.ca](mailto:sinclair@mcmaster.ca)

Henrik Verder, MD: Department of Paediatrics, Holbaek University Hospital, University of Copenhagen, Smedelundsgade 60, DK-4300 Holbaek, Denmark. Fax: +45 59484209, [hav@regionsjaelland.dk](mailto:hav@regionsjaelland.dk)

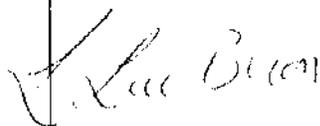
Wolfgang Lindner, MD: Universitäts-Kinderklinik Ulm, Sektion Neonatologie und Padiatrische Intensivmedizin, Primivstr. 43,89075 Ulm, Germany. Fax: +49 731 500 26739, [wolfgang.lindner@medizin.uni-ulm.de](mailto:wolfgang.lindner@medizin.uni-ulm.de)

Michael Dunn, MD: Department of Newborn and Developmental Pediatrics, Aubrey and Marla Dan Program for High Risk Mothers and Babies, Sunnybrook Health Sciences Centre, Room M4-222, 2075 Bayview Ave, Toronto, Ontario, Canada M4N 3M5; Fax: 416-323-6274, [michael.dunn@sunnybrook.ca](mailto:michael.dunn@sunnybrook.ca); [michael.dunn@sw.ca](mailto:michael.dunn@sw.ca)

Kajsa Bohlin, MD, Division of Pediatrics, B57, Karolinska University Hospital Huddinge, S-141 86 Stockholm, Sweden, Fax Fax: +46 8-31 11 01, [kajsa.bohlin@ki.se](mailto:kajsa.bohlin@ki.se)

We respectfully request to consider the attached manuscript for publication in Pediatrics. We believe this manuscript describes a study with strong design, which brings novel and significant findings that are relevant to the readership of Journal of Pediatrics.

Sincerely,



**Luc P. Brion, MD**

**Professor of Pediatrics**

**[Luc.brion@utsouthwestern.edu](mailto:Luc.brion@utsouthwestern.edu)**

**Telephone 214-648-3903; fax 214-648-2481**

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1,4</sup> Roy Heyne, MD,<sup>1</sup>  
Mambarambath Jaleel,<sup>1</sup> MD, Neil Finer, MD,<sup>5</sup> Waldemar A. Carlo, MD,<sup>6</sup>  
Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7</sup> Rosemary D. Higgins, MD,<sup>8</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: <sup>1</sup>Department of Pediatrics, University of Texas Southwestern, Dallas, TX; <sup>2</sup>Current affiliation: Pediatrix Medical Group, San Antonio, TX; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>4</sup>Current affiliation: The Ohio State University - Nationwide Children's Hospital; <sup>5</sup>Division of Neonatology, University of California, San Diego, CA; <sup>6</sup>Division of Neonatology, University of Alabama, Birmingham, AL; <sup>7</sup>Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; <sup>8</sup>*Eunice Kennedy Shriver* National Institute of Child, Health and Human Development, Bethesda, MD

Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu  
No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

Short title: Clinical practice changes after SUPPORT

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

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List of Abbreviations:

BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## **Abstract**

### **Objective**

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after publication of SUPPORT within NICUs in NRN centers.

### **Study Design:**

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### **Results:**

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

## **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

### Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

### Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

### Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was ETI in DR.

Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>7-16</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%,  $p<0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p<0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p<0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p=0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p=0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 2). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in the appendix. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p=0.18$ ).

### **Discussion:**

Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast

with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces

confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB did not include information on the rationale used for various practices used for each patient in each center. We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and

changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive-pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies. This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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## Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Difference in Means<sup>3</sup> (95% CI)</b>	<b>adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p value<sup>4</sup></b>
Intubated in delivery room (primary outcome)	1313 (81.2)	1539 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Appendix. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.0028
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

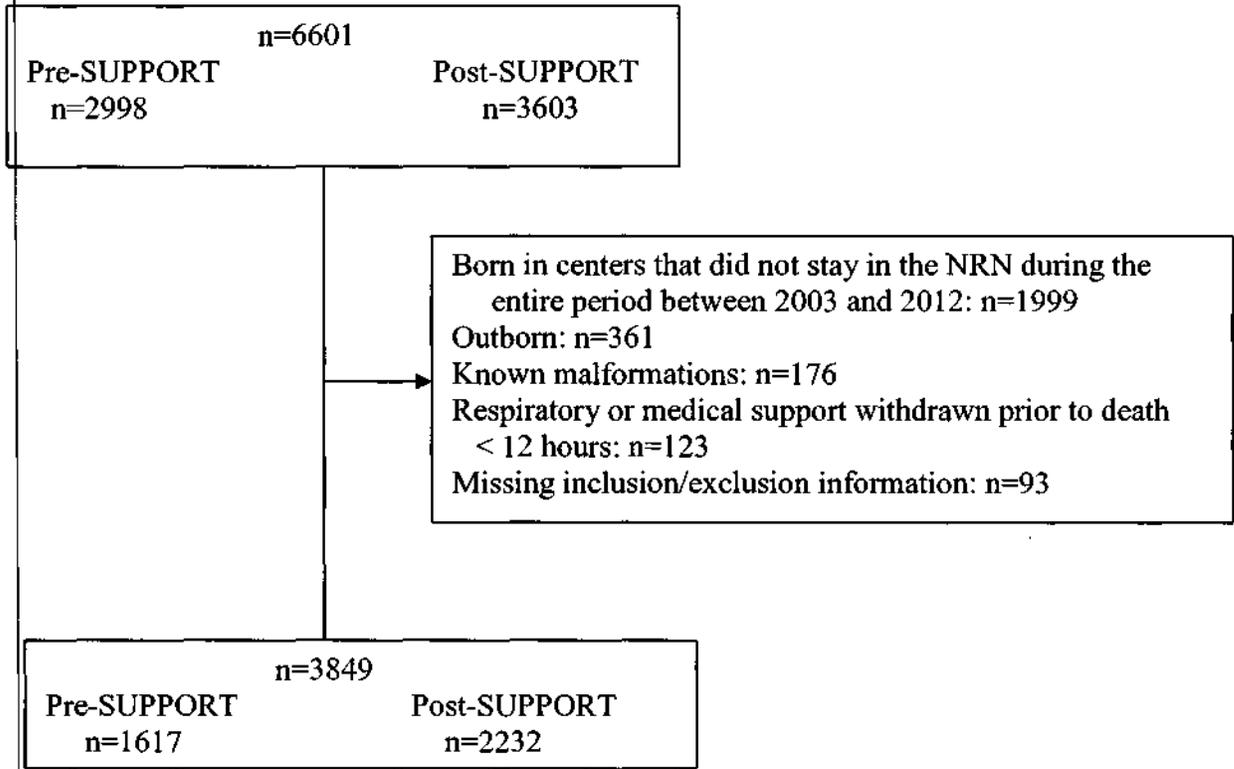
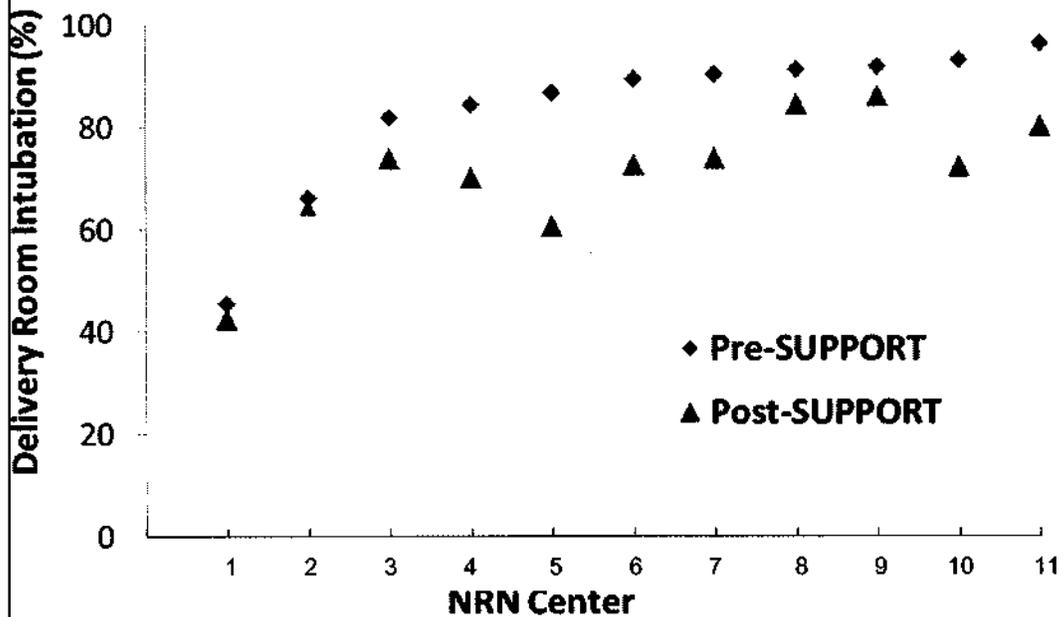


Figure 2



**From:** Lewis-Evans, Amanda  
**To:** alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy.newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher  
**Cc:** sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Becky Brazeal; Brenda Vecchio; Cunningham, Meg; Gabrio, Jenna; Huitema, Carolyn Petrie; Lewis-Evans, Amanda; Suzanne Sayers; Zaterka-Baxter, Kristin  
**Subject:** Support Subcommittee Call (10/2 Wednesday 11:00 AM ET)  
**Date:** Wednesday, September 11, 2013 1:37:34 PM

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Dear all,

The Support Subcommittee Call has been scheduled for:

**Wednesday, 10/2**  
**11:00 AM ET**

Dial:  
Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Unfortunately we were unable to find a time that worked with everyone's schedule, so Betty Vohr will be unable to attend.

Thanks,

Amanda

---

**From:** Lewis-Evans, Amanda  
**Sent:** Tuesday, August 27, 2013 2:22 PM  
**To:** [SCRN] Stoll, Barbara (barbara\_stoll@oz.ped.emory.edu); Bell, Edward; Das, Abhik (adas@rti.org); 'dstevenson@stanford.edu'; Gantz, Marie (mgantz@rti.org); goldb008@mc.duke.edu; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'jeff-murray@uiowa.edu'; john-dagle@uiowa.edu; Johnson, Karen; kurt.schibler@cchmc.org; McDonald, Scott A.; 'Michael Cotten'; Namasivayam Ambalavanan (nambalavanan@peds.uab.edu); Page, Grier; 'Sood, Beena'; vanmeurs@leland.stanford.edu; Wallace, Dennis; Whitehead, Nedra; Bill Truog; Leif Nelin; Pablo Sanchez (pablo.sanchez@nationwidechildrens.org); Uday Devaskar; Wally Carlo, M.D.; Anna Maria Hibbs; Brenda Poindexter (bpoindex@iu.edu); bvohr@wihri.org; DeMauro, Sara M; 'Kathleen.A.Kennedy@uth.tmc.edu'; Leslie Dawn Wilson (ldw@iu.edu); Tarah Colaizy; Wrage, Lisa Ann; Andi Duncan; Cheri Gauldin; 'Conra Lacy'; 'Erika Fernandez'; Greg Sokol (gsokol@iu.edu); Kendrick, Douglas E. (in StatEpi); kwatterberg@salud.unm.edu; Maky Fraga; mcw3@cwru.edu; Sandra Beauman; Abbot Laptook (alaptook@WIHRI.org); Bethany Ball; 'ellen\_hale@oz.ped.emory.edu'; nancy.newman; 'sshankar@med.wayne.edu'; Ann Marie Scorsone; Bob Ward (Robert.Ward@hsc.utah.edu); Carol Cole; 'dale\_rhels@urmc.rochester.edu'; Nolen, Tracy; Williams, Rick L.; 'woh@wihri.org'; Zaterka-Baxter, Kristin; apappas@med.wayne.edu; Cathy Grisby (cathy.grisby@uc.edu); 'claudia.pedroza@uth.tmc.edu'; jon.e.tyson@uth.tmc.edu; rbara@med.wayne.edu; Roy.Heyne@utsouthwestern.edu; Aasma Chaudhary; 'ahensman@wihri.org'; Huitema, Carolyn Petrie; Munoz, Breda; Bradley Yoder; Diana Vasil; Eggleston,

Barry; Joanna Beachy; Kevin Dysart; 'Matt Laughon'; Roger.Faix@hsc.utah.edu;  
'Georgia.E.McDavid@uth.tmc.edu'; Kevin Lally (Kevin.P.Lally@uth.tmc.edu); Marty Blakely;  
'rohls@salud.unm.edu'; 'srhinz@stanford.edu'; Gerry Taylor; Hammond, Jane (hammond@rti.org); Jean  
Lowe; Maureen Hack (mxh7@cwru.edu); 'nfiner@ucsd.edu'

**Cc:** Lewis-Evans, Amanda (alewis@rti.org); Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin;  
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'gonza025@mc.duke.edu'; 'jwaidne@emory.edu'; lisa.joo@stanford.edu; Sarah Barten; Becky Brazeel;  
Kristie Smiley; Garcia, Deborah; rrapozafarrands@wihri.org; Cunningham, Meg (mcunningham@rti.org);  
Lewis-Evans, Amanda; Zaterka-Baxter, Kristin (kzaterka@rti.org); 'Brenda Vecchio';  
'Imcore@med.wayne.edu'; (sharon.gough@hsc.utah.edu); Linda Mathieu; Michelle Smith  
(Nancy.M.Smith@uth.tmc.edu); Matthew Seckman; Robin Brown; Scottie Wahlstrom; Auman, Jeanette  
O.; Newman, Jamie; Suzanne Sayers

**Subject:** NRN Subcommittee Calls - Availability Request

Dear all,

We would like to schedule calls prior to the October SCM for the following subcommittees:

Genomics  
Publications  
MILK  
Term and Late Preterm Hypotension  
INS  
GDB  
OC  
Late Hypothermia  
Preemie Hypothermia  
NEST  
SUPPORT Neuro School Age

Please provide your availability for the following dates via email or using the **THREE** separate Doodle polls:

**PART 1:** <http://doodle.com/b33f5anfux2ynews>

9/3, Tu

9/4, W

9/5, Th

9/6, F

9/9, M

9/10, Tu

9/11, W

9/12, Th

9/13, F

**PART 2:** <http://doodle.com/r4eprd2hh8udkhbe>

9/16, M

9/17, Tu  
9/18, W  
9/19, Th  
9/20, F

9/23, M  
9/24, Tu  
9/25, W  
9/26, Th  
9/27, F

9/30, M

**PART 3:** <http://doodle.com/psbrvs3r5epfn52b>

10/1, Tu  
10/2, W  
10/3, Th  
10/4, F

10/7, M  
10/8, Tu  
10/9, W  
10/10, Th  
10/11, F

Thanks,

Amanda Lewis-Evans  
RTI International  
3040 Cornwallis Road  
312-D Cox Building  
Research Triangle Park, NC 27713  
Phone: 919-990-8483  
Fax: 919-541-6722

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "[Lewis-Evans, Amanda](#)"  
**Subject:** RE: Rose Please Read: Support Subcommittee Call - Availability Request  
**Date:** Wednesday, September 11, 2013 1:30:15 PM

---

No preference – either is fine

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Lewis-Evans, Amanda [<mailto:alewis@rti.org>]  
**Sent:** Wednesday, September 11, 2013 1:29 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** [alewis@rti.org](mailto:alewis@rti.org)  
**Subject:** Rose Please Read: Support Subcommittee Call - Availability Request

Hi Rose,

The best dates for the Support call are

Wednesday, Oct 2nd 11:00AM-12:00PM ET  
Not Available: Betty Vohr  
No Response: Gerry Taylor and Neil Finer

Thursday, Oct 3rd 12:00-1:00PM ET.  
Not Available: Betty Vohr  
No Response: Gerry Taylor and Neil Finer

Do you have a preference?

Thank you!

Amanda

**From:** Lewis-Evans, Amanda  
**Sent:** Tuesday, August 27, 2013 2:22 PM  
**To:** [SCRN] Stoll, Barbara ([barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu)); Bell, Edward; Das, Abhik ([adas@rti.org](mailto:adas@rti.org)); 'dstevenson@stanford.edu'; Gantz, Marie ([mgantz@rti.org](mailto:mgantz@rti.org));

[goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); 'Higgins, Rosemary (NIH/NICHD) [E]'; '[jeff-murray@uiowa.edu](mailto:jeff-murray@uiowa.edu)'; '[john-dagle@uiowa.edu](mailto:john-dagle@uiowa.edu)'; Johnson, Karen; '[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)'; McDonald, Scott A.; 'Michael Cotten'; Namasivayam Ambalavanan ([nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu)); Page, Grier; 'Sood, Beena'; '[yanmeurs@leland.stanford.edu](mailto:yanmeurs@leland.stanford.edu)'; Wallace, Dennis; Whitehead, Nedra; Bill Truog; Leif Nelin; Pablo Sanchez ([pablo.sanchez@nationwidechildrens.org](mailto:pablo.sanchez@nationwidechildrens.org)); Uday Devaskar; Wally Carlo, M.D.; Anna Maria Hibbs; Brenda Poindexter ([bpindex@iu.edu](mailto:bpindex@iu.edu)); '[bvohr@wihri.org](mailto:bvohr@wihri.org)'; DeMauro, Sara M; '[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)'; Leslie Dawn Wilson ([ldw@iu.edu](mailto:ldw@iu.edu)); Tarah Colaizy; Wrage, Lisa Ann; Andi Duncan; Cheri Gauldin; 'Conra Lacy'; 'Erika Fernandez'; Greg Sokol ([gsokol@iu.edu](mailto:gsokol@iu.edu)); Kendrick, Douglas E. (in StatEpi); '[kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)'; Maky Fraga; '[mcw3@cwru.edu](mailto:mcw3@cwru.edu)'; Sandra Beauman; Abbot Laptook ([alaptook@WIHRI.org](mailto:alaptook@WIHRI.org)); Bethany Ball; '[ellen\\_hale@oz.ped.emory.edu](mailto:ellen_hale@oz.ped.emory.edu)'; nancy newman; '[sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu)'; Ann Marie Scorsone; Bob Ward ([Robert.Ward@hsc.utah.edu](mailto:Robert.Ward@hsc.utah.edu)); Carol Cole; '[dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)'; Nolen, Tracy; Williams, Rick L.; '[woh@wihri.org](mailto:woh@wihri.org)'; Zaterka-Baxter, Kristin; '[apappas@med.wayne.edu](mailto:apappas@med.wayne.edu)'; Cathy Grisby ([cathy.grisby@uc.edu](mailto:cathy.grisby@uc.edu)); '[claudia.pedroza@uth.tmc.edu](mailto:claudia.pedroza@uth.tmc.edu)'; '[jone.tyson@uth.tmc.edu](mailto:jone.tyson@uth.tmc.edu)'; '[rbhara@med.wayne.edu](mailto:rbhara@med.wayne.edu)'; '[Roy.Heyne@utsouthwestern.edu](mailto:Roy.Heyne@utsouthwestern.edu)'; Aasma Chaudhary; '[ahensman@wihri.org](mailto:ahensman@wihri.org)'; Huitema, Carolyn Petrie; Munoz, Breda; Bradley Yoder; Diana Vasil; Eggleston, Barry; Joanna Beachy; Kevin Dysart; 'Matt Laughon'; '[Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)'; '[Georgia.E.McDavid@uth.tmc.edu](mailto:Georgia.E.McDavid@uth.tmc.edu)'; Kevin Lally ([Kevin.P.Lally@uth.tmc.edu](mailto:Kevin.P.Lally@uth.tmc.edu)); Marty Blakely; '[rohls@salud.unm.edu](mailto:rohls@salud.unm.edu)'; '[rhintz@stanford.edu](mailto:rhintz@stanford.edu)'; Gerry Taylor; Hammond, Jane ([hammond@rti.org](mailto:hammond@rti.org)); Jean Lowe; Maureen Hack ([mxh7@cwru.edu](mailto:mxh7@cwru.edu)); '[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)'  
Cc: 'Lewis-Evans, Amanda ([alewis@rti.org](mailto:alewis@rti.org))'; Gabrio, Jenna; Cunningham, Meg; Zaterka-Baxter, Kristin; ([debra.camputaro@yale.edu](mailto:debra.camputaro@yale.edu)); ([pamela.neville@duke.edu](mailto:pamela.neville@duke.edu)); 'Archer, Stephanie (NIH/NICHD) [E]'; '[gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu)'; '[jwaidne@emory.edu](mailto:jwaidne@emory.edu)'; '[lisa.joo@stanford.edu](mailto:lisa.joo@stanford.edu)'; Sarah Barten; Becky Brazeel; Kristie Smiley; Garcia, Deborah; '[rapozafarrands@wihri.org](mailto:rapozafarrands@wihri.org)'; Cunningham, Meg ([mcunningham@rti.org](mailto:mcunningham@rti.org)); Lewis-Evans, Amanda; Zaterka-Baxter, Kristin ([kzaterka@rti.org](mailto:kzaterka@rti.org)); 'Brenda Vecchio'; '[lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu)'; ([sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu)); Linda Mathieu; Michelle Smith ([Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu)); Matthew Seckman; Robin Brown; Scottie Wahlstrom; Auman, Jeanette O.; Newman, Jamie; Suzanne Sayers  
**Subject:** NRN Subcommittee Calls - Availability Request

Dear all,

We would like to schedule calls prior to the October SCM for the following subcommittees:

Genomics  
Publications  
MILK  
Term and Late Preterm Hypotension  
INS  
GDB  
OC  
Late Hypothermia  
Premie Hypothermia  
NEST  
SUPPORT Neuro School Age

Please provide your availability for the following dates via email or using the **THREE**

separate Doodle polls:

**PART 1:** <http://doodle.com/b33f5anfux2ynews>

9/3, Tu  
9/4, W  
9/5, Th  
9/6, F  
9/9, M  
9/10, Tu  
9/11, W  
9/12, Th  
9/13, F

**PART 2:** <http://doodle.com/r4eprd2hh8udkhbe>

9/16, M  
9/17, Tu  
9/18, W  
9/19, Th  
9/20, F

9/23, M  
9/24, Tu  
9/25, W  
9/26, Th  
9/27, F

9/30, M

**PART 3:** <http://doodle.com/psbrvs3r5epfn52b>

Both suite me for the school age follow up call, Maureen Hack

10/1, Tu  
10/2, W  
10/3, Th  
10/4, F

10/7, M  
10/8, Tu  
10/9, W  
10/10, Th  
10/11, F

Thanks,  
Amanda Lewis-Evans  
RTI International  
3040 Cornwallis Road  
312-D Cox Building

Research Triangle Park, NC 27713  
Phone: 919-990-8483  
Fax: 919-541-6722

--

Dr. Maureen Hack  
Professor of Pediatrics  
Case Western Reserve University  
Rainbow Babies and Children's Hospital  
University Hospitals of Cleveland  
11100 Euclid Avenue  
Cleveland, OH 44106-6010  
Phone 216 8443387  
Fax 216 8443380  
Email [mxh7@case.edu](mailto:mxh7@case.edu)

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 11:34 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I'm just wondering if when I said (b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 9:29 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Not sure what you mean. I sent her this response to clarify the confusion between IRS and institutions (call me on 301-675-2920 if you want to chat):

Sorry if this wasn't clear. You asked how many (b)(5)

(b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 9:27 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Which one, the 9<sup>th</sup>?

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, September 11, 2013 8:57 AM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Bob:

Yes, I think she is (b)(5)

(b)(5)

Thanks,  
Renate

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 8:53 AM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate, I'm thinking I (b)(5)

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Tuesday, September 10, 2013 9:00 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

Just want to confirm the answer to the first question is "Yes, that's correct". Also see her second request.

Sent from my BlackBerry 10 smartphone.

**From:** Skeen, Kim  
**Sent:** Tuesday, September 10, 2013 8:10 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate,

When you say "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.

On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).

I will be at my desk Wednesday morning if you would like to give me a call. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Monday, September 09, 2013 9:24 PM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Apologies, again, for the delay; following are responses to your questions attributable to NIH generally:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

There were 25 IRBs overseeing the institutions in the Neonatal Research Network at the time the SUPPORT Study was undertaken, including the one at the Data Coordinating Center (RTI); however, the Data Coordinating Center did not see patients and so it did not produce a consent form for the study and its IRB did not review one. Therefore, it is accurate to say that IRBs for each of the institutions taking part in the study (24 in all) each reviewed consent forms for the institutions they served.

The Data Coordinating Center did have its IRB review its role in coordinating the SUPPORT study data. But as noted above, the Data Coordinating Center's IRB did not review or approve a patient consent form for the SUPPORT study because the Center's role is to coordinate data, not to see patients.

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

Results data associated with various published studies on the SUPPORT trial are publicly available in the journals in which the studies were published. Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites.

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

There are several surfactants available in the U.S. and the type of surfactant was determined by the individual sites and not dictated by the protocol. Information on which surfactant formulation a site used may be available from that site. It may help you to know that in its letter to the University of Alabama last March, OHRP noted that it was not concerned with the arm of the study comparing surfactant treatment to CPAP.

Best,  
Renate

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

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Monday, September 09, 2013 6:19 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Renate,

We are still looking for answers to the questions we submitted last week (see below). Please provide a response.

- What is the correct number of IRB's for the SUPPORT study? We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Thank you.

Regards,

Kim

Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
skeenk@cbsnews.com

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

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]  
Sent: Friday, September 06, 2013 12:36 PM  
To: Skeen, Kim  
Subject: Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

From: Skeen, Kim  
Sent: Friday, September 6, 2013 12:27 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]  
Sent: Friday, September 06, 2013 11:17 AM  
To: Skeen, Kim  
Subject: RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:

<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

Renate Myles, MBA  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [mylesr@mail.nih.gov](mailto:mylesr@mail.nih.gov)<<mailto:mylesr@mail.nih.gov>>  
Web: <http://www.nih.gov><<http://www.nih.gov>>

NIH . . . Turning Discovery Into Health

Celebration of Science at NIH<<http://www.youtube.com/watch?v=gYkP9ED5naA>>: watch how medical research saves lives and improves health

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Thursday, September 05, 2013 12:39 PM  
To: Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
Cc: Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
Subject: CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Thursday, September 05, 2013 11:33 AM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

· NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.

· RTI's NIH funding information is publicly available from NIH.

· The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Thursday, September 05, 2013 11:23 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Lisa,  
Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Skeen, Kim  
Sent: Wednesday, September 04, 2013 3:09 PM  
To: 'Bistreich-Wolfe, Lisa'  
Subject: RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're

working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Wednesday, September 04, 2013 3:02 PM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Wednesday, September 04, 2013 11:53 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

From: Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
Sent: Wednesday, September 04, 2013 11:24 AM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

We are aware of concerns voiced about the informed consent document regarding this particular study.

. RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.

. As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
www.rti.org/newsroom

-----  
From: Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
Sent: Tuesday, September 03, 2013 4:55:51 PM  
To: News  
Subject: CBS News is trying to reach you Auto forwarded by a Rule

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
skeenk@cbsnews.com<mailto:skeenk@cbsnews.com>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: CBS News questions regarding RTI  
**Date:** Wednesday, September 11, 2013 7:16:35 AM

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One more item- the oxmeters were purchased from Massimo

Sent from my iPhone

On Sep 11, 2013, at 6:56 AM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Okay, thanks.

Sent from my BlackBerry 10 smartphone.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, September 11, 2013 6:19 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: CBS News questions regarding RTI

---

As far as I know, (b)(5)

(b)(5)

Sent from my iPhone

On Sep 10, 2013, at 8:59 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Just want to confirm the answer to the first question is "Yes, that's correct". Also see her second request.

Sent from my BlackBerry 10 smartphone.

---

**From:** Skeen, Kim  
**Sent:** Tuesday, September 10, 2013 8:10 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

---

Renate,

When you say: "Individual patient-level data have not been shared outside of the NICHD Neonatal Research network sites" we take that to mean that you are confirming that no corporate entities, such as pharmaceutical or device firms, received this information or had any direct or indirect interest in the SUPPORT study. If this is NOT correct, please let us know.

On the surfactant question, can someone have a very brief conversation with my correspondent Sharyl Attkisson about this? (She has a few background questions including why the brand/type of surfactant used would not possibly affect the results).

I will be at my desk Wednesday morning if you would like to give me a call. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Monday, September 09, 2013 9:24 PM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

Apologies, again, for the delay; following are responses to your questions attributable to NIH generally:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

There were 25 IRBs overseeing the institutions in the Neonatal Research Network at the time the SUPPORT Study was undertaken, including the one at the Data Coordinating Center (RTI); however, the Data Coordinating Center did not see patients and so it did not produce a consent form for the study and its IRB did not review one. Therefore, it is accurate to say that IRBs for each of the institutions taking part in the study (24 in all) each reviewed consent forms for the institutions they served.

The Data Coordinating Center did have its IRB review its role in coordinating the SUPPORT study data. But as noted above, the Data Coordinating Center's IRB did not review or approve a patient consent form for the SUPPORT study because the Center's role is to coordinate data, not to see patients.

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

Results data associated with various published studies on the SUPPORT trial are publicly available in the journals in which the studies were published. Individual patient-level data have not been shared outside of the NICHD

Neonatal Research network sites.

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

There are several surfactants available in the U.S. and the type of surfactant was determined by the individual sites and not dictated by the protocol. Information on which surfactant formulation a site used may be available from that site. It may help you to know that in its letter to the University of Alabama last March, OHRP noted that it was not concerned with the arm of the study comparing surfactant treatment to CPAP.

Best,  
Renate

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

From: Skeen, Kim [mailto:SkeenK@cbsnews.com]  
Sent: Monday, September 09, 2013 6:19 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Renate,

We are still looking for answers to the questions we submitted last week (see below). Please provide a response.

- What is the correct number of IRB's for the SUPPORT study? We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Thank you.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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

From: Myles, Renate (NIH/OD) [E]  
[<mailto:mylesr@od.nih.gov>]  
Sent: Friday, September 06, 2013 12:36 PM  
To: Skeen, Kim  
Subject: Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

From: Skeen, Kim  
Sent: Friday, September 6, 2013 12:27 PM  
To: Myles, Renate (NIH/OD) [E]  
Subject: RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Myles, Renate (NIH/OD) [E]  
[<mailto:mylesr@od.nih.gov>]  
Sent: Friday, September 06, 2013 11:17 AM  
To: Skeen, Kim  
Subject: RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the

Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Friday, September 06, 2013 10:57 AM  
To: Myles, Renate (NIH/OD) [E]  
Subject: FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?
- o We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).
- o Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per

patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

Renate Myles, MBA  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [mylesr@mail.nih.gov](mailto:mylesr@mail.nih.gov)<<mailto:mylesr@mail.nih.gov>>  
Web: <http://www.nih.gov><<http://www.nih.gov/>>

NIH . . . Turning Discovery Into Health

Celebration of Science at  
NIH<<http://www.youtube.com/watch?v=gYkP9ED5naA>>: watch  
how medical research saves lives and improves health

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Thursday, September 05, 2013 12:39 PM  
To: Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
Cc: Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
Subject: CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
Sent: Thursday, September 05, 2013 11:33 AM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Thursday, September 05, 2013 11:23 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday.  
We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Skeen, Kim  
Sent: Wednesday, September 04, 2013 3:09 PM  
To: 'Bistreich-Wolfe, Lisa'

Subject: RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
Sent: Wednesday, September 04, 2013 3:02 PM  
To: Skeen, Kim  
Cc: Spangenberg, Kami  
Subject: RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

From: Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
Sent: Wednesday, September 04, 2013 11:53 AM  
To: Bistreich-Wolfe, Lisa  
Subject: RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau

202-457-4383 office

(b)(5) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<<mailto:skeenk@cbsnews.com>>

From: Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

Sent: Wednesday, September 04, 2013 11:24 AM

To: Skeen, Kim

Cc: Spangenberg, Kami

Subject: RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

-----  
From: Skeen, Kim [[SMTP:SKEENK@CBSNEWS.COM](mailto:SKEENK@CBSNEWS.COM)]

Sent: Tuesday, September 03, 2013 4:55:51 PM

To: News

Subject: CBS News is trying to reach you Auto forwarded by a Rule

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)<mailto:skeenk@cbsnews.com>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: List of universities in the network  
**Date:** Wednesday, September 11, 2013 6:20:40 AM

---

Correct

Sent from my iPhone

On Sep 10, 2013, at 8:55 PM, "Myles, Renate (NIH/OD) [E]" <mylesr@od.nih.gov> wrote:

Hi Bob and Rose:

(b)(5) Can you look at my response to  
make sure I haven't misspoken?

Thanks,  
Renate

Hi Kim:

(b)(5)

Thanks  
Renate

Sent from my BlackBerry 10 smartphone.

---

**From:** Skeen, Kim  
**Sent:** Tuesday, September 10, 2013 8:07 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: List of universities in the network

---

Renate,

Today, we received the attached list of 20 institutions that took part in the SUPPORT

study. I would refer you to your previous email statement from Monday (see excerpt below) saying there were 24 institutions--why did we only get a list of 20? Please clarify. Thank you.

There were 25 IRBs overseeing the institutions in the Neonatal Research Network at the time the SUPPORT Study was undertaken, including the one at the Data Coordinating Center (RTI); however, the Data Coordinating Center did not see patients and so it did not produce a consent form for the study and its IRB did not review one. Therefore, it is accurate to say that IRBs for each of the institutions taking part in the study (24 in all) each reviewed consent forms for the institutions they served.

The Data Coordinating Center did have its IRB review its role in coordinating the SUPPORT study data. But as noted above, the Data Coordinating Center's IRB did not review or approve a patient consent form for the SUPPORT study because the Center's role is to coordinate data, not to see patients.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(5) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bock, Robert (NIH/NICHD) [E] [<mailto:bockr@exchange.nih.gov>]  
**Sent:** Tuesday, September 10, 2013 4:38 PM  
**To:** Skeen, Kim  
**Cc:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: List of universities in the network

Hi Kim. Renate asked me to send you the attached listing of the institutions that took part in the SUPPORT study.

Regarding the consent forms, for the 20 institutions listed, Cincinnati Children's Hospital had an additional form for University of Cincinnati Hospital and one for Good Samaritan Hospital; the University of California had an additional consent form for Sharp Mary Birch Hospital and the Utah site had an additional consent form for LDS Hospital.

I hope this is helpful.

Bob Bock

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, September 10, 2013 1:01 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: List of universities in the network  
**Attachments:** SUPPORT Recruiting Centers.doc

Was just checking with Rose. Here's what I have.

(b)(5)

## **SUPPORT Recruiting Centers**

### **Alpert Medical School of Brown University**

- Women & Infants Hospital of Rhode Island

### **Case Western Reserve University**

- Rainbow Babies & Children's Hospital

### **Cincinnati Children's Hospital Medical Center**

- University of Cincinnati Hospital
- Good Samaritan Hospital

### **Duke University School of Medicine**

- University Hospital
- Alamance Regional Medical Center
- Durham Regional Hospital

### **Emory University**

- Children's Healthcare of Atlanta
- Grady Memorial Hospital
- Emory Crawford Long Hospital

### **Indiana University**

- Indiana University Hospital
- Methodist Hospital
- Riley Hospital for Children
- Wishard Health Services

### **Stanford University**

- Lucile Packard Children's Hospital

### **Tufts Medical Center**

- Floating Hospital for Children

### **University of Alabama at Birmingham Health System**

- Children's Hospital of Alabama

### **University of California – San Diego Medical Center**

- Sharp Mary Birch Hospital for Women

### **University of Iowa Children's Hospital**

### **University of Miami Holtz Children's Hospital**

**University of New Mexico Health Sciences Center**

**University of Rochester Medical Center Golisano Children's Hospital**

**University of Texas Southwestern Medical Center at Dallas**

- Parkland Health & Hospital System
- Children's Medical Center Dallas

**University of Texas Health Science Center at Houston Medical School**

- Children's Memorial Hermann Hospital

**University of Utah Medical Center**

- Intermountain Medical Center
- LDS Hospital
- Primary Children's Medical Center

**Wake Forest University**

- Baptist Medical Center Brenner Children's Hospital
- Forsyth Medical Center

**Wayne State University**

- Hutzel Women's Hospital
- Children's Hospital of Michigan (U10 HD21385)

**Yale University**

- Yale-New Haven Children's Hospital
- Bridgeport Hospital

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: List of universities in the network  
**Date:** Tuesday, September 10, 2013 11:37:37 AM  
**Attachments:** SUPPORT Recruiting Centers.doc

---

Here is a list of the clinical sites – RTI also participated as the DCC

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, September 10, 2013 10:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: List of universities in the network

Hi Rose. Please see the note at the bottom. I just copied this from the back of the article. Is this a complete list?

The following are the authors' affiliations: the Division of Neonatology, University of Alabama at Birmingham, Birmingham (W.A.C., N.A.); the University of California at San Diego, San Diego (N.N.F., W.R.); the Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland (M.C.W., N.S.N.); the Statistics and Epidemiology Unit, RTI International, *ReTh* *e new england journal of medicine* 10.1056/nejmoa0911781 [nejm.org](http://nejm.org) search Triangle Park (M.G.G., W.K.P.), the Department of Pediatrics, Duke University, Durham (C.M.C.), and Wake Forest University School of Medicine, Winston-Salem (T.M.O.) — all in North Carolina; the Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI (A.R.L.); the Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City (B.A.Y., R.G.F.); the Statistics and Epidemiology Unit, RTI International, Rockville (A.D.), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health,

Bethesda (R.D.H.) — both in Maryland;  
the Department of Pediatrics, University of Cincinnati, Cincinnati (K.S., V.N.); the Department of  
Pediatrics, Division of Newborn  
Medicine, Floating Hospital for Children, Tufts Medical Center, Boston (I.D.F.); the Department of  
Pediatrics, University of Texas  
Southwestern Medical Center, Dallas (P.J.S.); the Department of Pediatrics, Emory University School  
of Medicine, and Children's  
Healthcare of Atlanta — both in Atlanta (A.J.P.); the Department of Pediatrics, University of Texas  
Medical School at Houston, Houston  
(B.H.M.); the University of Rochester School of Medicine and Dentistry, Rochester, NY (N.L., D.L.P.);  
the Department of Pediatrics,  
Indiana University School of Medicine, Indianapolis (B.B.P.); the Department of Pediatrics, Stanford  
University School of Medicine, Palo  
Alto, CA (K.P.V.M.); the University of Miami Miller School of Medicine, Miami (S.D.); the Department  
of Pediatrics, Wayne State University,  
Detroit (B.G.S.); the Department of Pediatrics, University of Iowa, Iowa City (E.F.B.); the Department  
of Pediatrics, Yale University  
School of Medicine, New Haven, CT (R.A.E.); and the University of New Mexico Health Sciences  
Center, Albuquerque (K.L.W.).  
The following investigators, in addition to those listed as authors, participated in this study: Neonatal  
Research Network Steering

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Tuesday, September 10, 2013 10:43 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** List of universities in the network

Hi Bob:

I just got off the phone with Kim Skeen and she asked if we could just send her a list of the organizations who participated in the study at the time. I agree with her that figuring it out from the NEJM's article is nearly impossible given all of the affiliated organizations listed. Can you pull the relevant organizations and send to me today (or to her with copy to me)?

Thanks,  
Renate

## **SUPPORT Recruiting Centers**

### **Alpert Medical School of Brown University**

- Women & Infants Hospital of Rhode Island

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- Rainbow Babies & Children's Hospital

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- University of Cincinnati Hospital
- Good Samaritan Hospital

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- Durham Regional Hospital

### **Emory University**

- Children's Healthcare of Atlanta
- Grady Memorial Hospital
- Emory Crawford Long Hospital

### **Indiana University**

- Indiana University Hospital
- Methodist Hospital
- Riley Hospital for Children
- Wishard Health Services

### **Stanford University**

- Lucile Packard Children's Hospital

### **Tufts Medical Center**

- Floating Hospital for Children

### **University of Alabama at Birmingham Health System**

- Children's Hospital of Alabama

### **University of California – San Diego Medical Center**

- Sharp Mary Birch Hospital for Women

### **University of Iowa Children's Hospital**

### **University of Miami Holtz Children's Hospital**

**University of New Mexico Health Sciences Center**

**University of Rochester Medical Center Golisano Children's Hospital**

**University of Texas Southwestern Medical Center at Dallas**

- Parkland Health & Hospital System
- Children's Medical Center Dallas

**University of Texas Health Science Center at Houston Medical School**

- Children's Memorial Hermann Hospital

**University of Utah Medical Center**

- Intermountain Medical Center
- LDS Hospital
- Primary Children's Medical Center

**Wake Forest University**

- Baptist Medical Center Brenner Children's Hospital
- Forsyth Medical Center

**Wayne State University**

- Hutzel Women's Hospital
- Children's Hospital of Michigan (U10 HD21385)

**Yale University**

- Yale-New Haven Children's Hospital
- Bridgeport Hospital

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fwd: List of universities in the network  
**Date:** Tuesday, September 10, 2013 11:04:32 AM

---

Can you send me a list of the sites with each of the recruiting hospitals for support? ASAP please

Sent from my iPhone

Begin forwarded message:

**From:** "Bock, Robert (NIH/NICHD) [E]" <[bockr@exchange.nih.gov](mailto:bockr@exchange.nih.gov)>  
**Date:** September 10, 2013, 10:51:52 AM EDT  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**Cc:** "Childress, Kerri (NIH/NICHD) [E]" <[kerri.childress@nih.gov](mailto:kerri.childress@nih.gov)>  
**Subject:** RE: List of universities in the network

Hi Rose. Please see the note at the bottom. I just copied this from the back of the article. Is this a complete list?

The following are the authors' affiliations: the Division of Neonatology, University of Alabama at Birmingham, Birmingham (W.A.C., N.A.); the University of California at San Diego, San Diego (N.N.F., W.R.); the Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland (M.C.W., N.S.N.); the Statistics and Epidemiology Unit, RTI International, *ReTh* *e new england journal of medicine* 10.1056/nejmoa0911781 [nejm.org](http://nejm.org) search Triangle Park (M.G.G., W.K.P.), the Department of Pediatrics, Duke University, Durham (C.M.C.), and Wake Forest University School of Medicine, Winston-Salem (T.M.O.) — all in North Carolina; the Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI (A.R.L.); the Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City (B.A.Y., R.G.F.); the Statistics and Epidemiology Unit, RTI International, Rockville (A.D.), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda (R.D.H.) — both in Maryland; the Department of Pediatrics, University of Cincinnati, Cincinnati (K.S., V.N.); the Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston (I.D.F.); the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas (P.J.S.); the Department of Pediatrics, Emory University School of Medicine, and Children's Healthcare of Atlanta — both in Atlanta (A.J.P.); the Department of Pediatrics,

University of Texas Medical School at Houston, Houston (B.H.M.); the University of Rochester School of Medicine and Dentistry, Rochester, NY (N.L., D.L.P.); the Department of Pediatrics, Indiana University School of Medicine, Indianapolis (B.B.P.); the Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA (K.P.V.M.); the University of Miami Miller School of Medicine, Miami (S.D.); the Department of Pediatrics, Wayne State University, Detroit (B.G.S.); the Department of Pediatrics, University of Iowa, Iowa City (E.F.B.); the Department of Pediatrics, Yale University School of Medicine, New Haven, CT (R.A.E.); and the University of New Mexico Health Sciences Center, Albuquerque (K.L.W.).

The following investigators, in addition to those listed as authors, participated in this study: Neonatal Research Network Steering

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Tuesday, September 10, 2013 10:43 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** List of universities in the network

Hi Bob:

I just got off the phone with Kim Skeen and she asked if we could just send her a list of the organizations who participated in the study at the time. I agree with her that figuring it out from the NEJM's article is nearly impossible given all of the affiliated organizations listed. Can you pull the relevant organizations and send to me today (or to her with copy to me)?

Thanks,  
Renate

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, September 10, 2013 11:02 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: List of universities in the network

Checking with Rose.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Tuesday, September 10, 2013 10:43 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** List of universities in the network

Hi Bob:

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Thanks,  
Renate

**From:** Luc Brion  
**To:** "doctorlevan@gmail.com"; "Wrage, Lisa Ann"; "Barbara Stoll"; "nfiner@ucsd.edu"; "Wally Carlo, M.D."; Roy Heyne; "Gantz, Marie"; Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Gantz, Marie"; Mambarambath Jaleel; Myra Wyckoff; "Pablo.Sanchez@nationwidechildrens.org"  
**Subject:** Updated manuscript on changes after SUPPORT for Journal of Pediatrics  
**Date:** Monday, September 09, 2013 6:08:58 PM  
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Roy, Lisa, Jackie et al:

Thanks for all the comments and suggestions.

I made several additional changes to fit requirements for Journal of Pediatrics.

I attach for your review a revised version manuscript for J Peds (one with edits and one clean version) and the letter of submission.

Best regards,

Luc

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**Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

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**Short title:** Clinical practice changes after SUPPORT

**Key words:** very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

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List of Abbreviations:

**BPD**, bronchopulmonary dysplasia;

**CI**, confidence interval;

**CPAP**, continuous positive airway pressure;

**DR**, delivery room;

**ETI**-Endotracheal Intubation;

**GA**, gestational age;

**GDB**, generic database;

**NRN**, Neonatal Research Network;

**PDA**, patent ductus arteriosus;

**PMA**, postmenstrual age;

**ROP**, retinopathy of prematurity;

**RR**, relative risk;

**SUPPORT**, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

## **Abstract**

### **Objective**

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1)

delivery room (DR) continuous positive airway pressure (CPAP) or intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%.

The objective of the current study was to compare medical care practices and neonatal outcomes before and after publication of SUPPORT within NICUs in NRN centers.

### **Study Design:**

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-12.

We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### **Results:**

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% confidence interval [CI] 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99)

and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

**Conclusions:**

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

## **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks postmenstrual age (PMA) was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen saturation target groups. However, the risk of death was higher

and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

### Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

### Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

### Baseline variables

Neonatal and maternal characteristics included birth weight, GA, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Outcome variables:

The primary outcome variable was ETI in DR.

Secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of PMA, the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to those used for the primary outcome of SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

Tertiary outcomes included practice variables such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus (PDA) and feeding practice, and the following outcome variables (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, DR outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage, oxygen supplementation, PDA, feeding and weight related variables, proven necrotizing enterocolitis (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

### Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for the primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes and NRN center), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.<sup>7-16</sup> Since we did not adjust p value for multiple comparisons, all secondary and tertiary analyses should be considered as exploratory.

A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks GA were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were excluded because they were born in NRN centers that did not participate in the NRN for the full duration of the study; and an additional 361 were excluded because they were outborn. Of the remaining infants, 176 infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1.

There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and less prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 2). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe

ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 2). In contrast, the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Unadjusted comparisons of tertiary outcome variables are shown in the appendix. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p=0.18$ ).

### **Discussion:**

Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast

with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are added. We elected to limit this study to centers that remained in the NICHD NRN during the two cohorts because of large inter-institutional differences observed in previous NRN studies; this allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Other limitations of this study include the observational design, which introduces

confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period; they differed from those used in SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size led to the finding of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB did not include information on the rationale used for various practices used for each patient in each center. We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the limited number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and

changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and prophylaxis of PDA,<sup>23-25</sup> synchronized nasal intermittent positive-pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of PDA may have changed based on results of other studies. This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that centers participating in SUPPORT might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Abhik Das:** Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Barbara Stoll:** Dr Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Rosemary Higgins:** Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011);

Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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## Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

<b>Characteristic</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Birth weight (grams)	825 (191)	818 (194)	0.32
GA (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

Abbreviation: GA, gestational age

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary and Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Difference in Means <sup>3</sup> (95% CI)	adjusted RR <sup>3</sup> (95% CI)	Adjusted p value <sup>4</sup>
Intubated in delivery room (primary outcome)	1313 (81.2)	1539 (69.0)	<0.0001		0.88 (0.85-0.91)	<0.0001
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe ROP	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors)	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk

<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account GA, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and NRN center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, PDA ligation, PDA indomethacin treatment, and late onset sepsis.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Appendix. Tertiary Outcomes<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352 /1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
ROP: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
ROP: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
ROP: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
PDA	795/1604 (49.6)	984/2203 (44.7)	0.0028
PDA, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
PDA, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
PDA ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks PMA (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity

<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup>survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

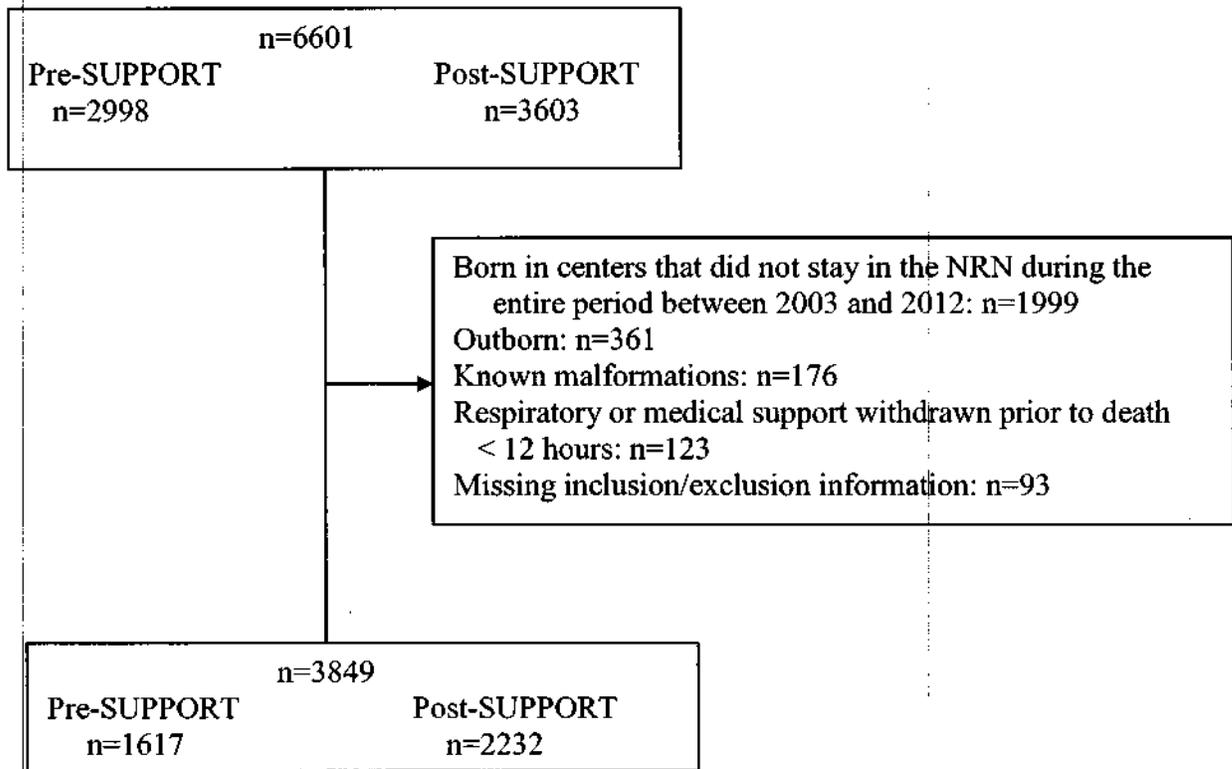
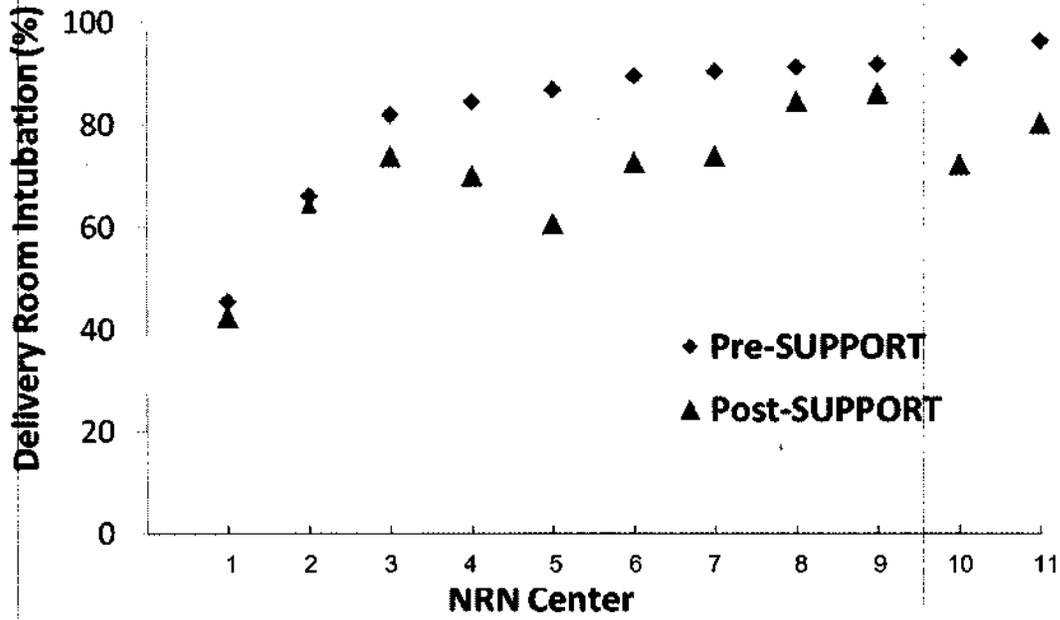


Figure 2



**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Great, thanks.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, September 09, 2013 1:02 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

(b)(5)

Rosemary D. Higgins, MD  
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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 1:00 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Rose:

Just to clarify, the relevant data was available with all of the studies below, correct? Since there are multiple studies, should we say:

(b)(5)

Thanks,  
Renate

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, September 09, 2013 12:01 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Bob's sentence is accurate:

The data showing the results from the SUPPORT study appeared in the New England Journal article describing the study's findings. The complete data set from the study has not been shared outside of the NICHD Neonatal Research network sites.

Here are the publications thus far from the SUPPORT Trial:

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Lupton AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010 May 27;362(21):1959-69. Epub 2010 May 16.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Lupton AR, Yoder BA, Faix RG, Das A, Poole WK, Donovan EF, Newman NS, Ambalavanan N, Frantz ID 3rd, Buchter S, Sánchez PJ, Kennedy KA, Laroia N, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, Higgins RD. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010 May 27;362(21):1970-9. Epub 2010 May 16.

Rich WD, Auten KJ, Gantz MG, Hale EC, Hensman AM, Newman NS, Finer NN; National Institute of Child Health and Human Development Neonatal Research Network. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics*. 2010 Jul;126(1):e215-21. Epub 2010 Jun 29.

Di Fiore JM, Walsh M, Wrage L, Rich W, Finer N, Carlo WA, Martin RJ; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Low Oxygen Saturation Target Range is Associated with Increased Incidence of Intermittent Hypoxemia. *J Pediatr*. 2012 Dec;161(6):1047-1052.e1. doi: 10.1016/j.jpeds.2012.05.046. Epub 2012 Jun 26.

Rich W, Finer NN, Gantz MG, Newman NS, Hensman AM, Hale EC, Auten KJ, Schibler K, Faix RG, Lupton AR, Yoder BA, Das A, Shankaran S; SUPPORT and Generic Database Subcommittees of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics*. 2012 Mar;129(3):480-4. Epub 2012 Feb 27.

Additional publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Vaucher YE, Peralta-Carcelen M, Finer NN, Carlo WA, Gantz MG, Walsh MC, Lupton AR, Yoder BA, Faix RG, Das A, Schibler K, Rich W, Newman NS, Vohr BR, Yolton K, Heyne RJ, Wilson-Costello DE, Evans PW, Goldstein RF, Acarregui MJ, Adams-Chapman I, Pappas A, Hintz SR, Poindexter B, Dusick AM, McGowan EC, Ehrenkranz RA,

Bodnar A, Bauer CR, Fuller J, O'Shea TM, Myers GJ, Higgins RD; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012 Dec 27;367(26):2495-504. doi: 10.1056/NEJMoa1208506.

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Monday, September 09, 2013 11:26 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Rose will need to clarify, so I've cc'd her.

We believed the reporter to be asking about the study's complete set of \_raw\_ data, not the de-identified data as it appeared in the article.

FYI, the NRN Steering Committee had received an earlier request from Public Citizen's asking for the complete data set and had turned down this request. (We have a copy of the NRN's response if you need it.)

So, to clarify in response to KH's request, you could state that:

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 11:02 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: TIME SENSITIVE FOR REVIEW: SUPPORT Study  
**Importance:** High

Hi Bob:

Can you check the wording on the data question per Kathy's notes? It may just need some caveats inserted.

Thanks,  
Renate

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 10:59 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

See note in red.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 4:57 PM  
**To:** Hudson, Kathy (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

Kim Skeen of CBS had some additional follow up questions. The proposed answers are included below for your review (NICHD has reviewed it).

ADD

Kim Skeen had additional questions:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

(b)(5)

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

(b)(5)

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

(b)(5)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Monday, September 09, 2013 11:31 AM  
**To:** Carey, Curtis (NIH/NIAAAA) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Here's where we are now with the responses to the CBS producer regarding the SUPPORT Study.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Monday, September 09, 2013 11:26 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Rose will need to clarify, so I've cc'd her.

We believed the reporter to be asking about the study's complete set of \_raw\_ data, not the de-identified data as it appeared in the article.

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So, to clarify in response to KH's request, you could state that:

(b)(5)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 11:02 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: TIME SENSITIVE FOR REVIEW: SUPPORT Study  
**Importance:** High

Hi Bob:

Can you check the wording on the data question per Kathy's notes? It may just need some caveats inserted.

Thanks,  
Renate

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Monday, September 09, 2013 10:59 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD)

[E]

**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

See note in red.

**From:** Myles, Renate (NIH/OD) [E]

**Sent:** Friday, September 06, 2013 4:57 PM

**To:** Hudson, Kathy (NIH/OD) [E]

**Cc:** Burklow, John (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]

**Subject:** RE: TIME SENSITIVE FOR REVIEW: SUPPORT Study

Hi Kathy:

Kim Skeen of CBS had some additional follow up questions. The proposed answers are included below for your review (NICHD has reviewed it).

ADD

Kim Skeen had additional questions:

**We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?**

(b)(5)

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

(b)(5)

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

(b)(5)

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Revised manuscript for Journal of Pediatrics  
**Date:** Sunday, September 08, 2013 3:26:04 PM

---

Rose:

One more question for you:

I presume I should check that we intend to publish open access since this paper was funded by NIH. Am I correct?

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern  
Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-9063  
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luc.brion@utsouthwestern.edu

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Saturday, September 07, 2013 5:08 PM  
**To:** Luc Brion  
**Subject:** Automatic reply: Revised manuscript for Journal of Pediatrics

I am out of the office on the morning of September 9 with no email access. If you need to reach someone else, please call 301-496-5575 and someone in the pregnancy and perinatology branch will assist you.

Rosemary D Higgins, MD  
Program Scientist

---

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Tai, Betty \(NIH/NIDA\) \[E\]](#)  
**Subject:** Re: SUPPORT study  
**Date:** Sunday, September 08, 2013 9:25:34 AM

---

Yes

Sent from my iPhone

On Sep 8, 2013, at 5:34 AM, "Tai, Betty (NIH/NIDA) [E]" <btai@nida.nih.gov> wrote:

- > As a subject of recent HHS hearing. Very interesting regarding the safety of standard care. R U familiar with the case?
- > Betty

**From:** Luc Brion  
**To:** "doctorlevan@gmail.com"; "Wrage, Lisa Ann"; "Barbara Stoll"; "nfiner@ucsd.edu"; "Wally Carlo, M.D."; Roy Heyne; "Gantz, Marie"; Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"; "Gantz, Marie"; Mambarambath Jaleel; Myra Wyckoff; Pablo.Sanchez@nationwidechildrens.org  
**Subject:** Revised manuscript for Journal of Pediatrics  
**Date:** Saturday, September 07, 2013 6:07:59 PM  
**Attachments:** Jackie LeVan Manuscript NRN 09-07-13.doc  
Letter of submission.docx  
peds20131595\_2brigs (2) corrections LPB.pdf

---

Hi everyone;

Thanks for all the comments.

I have revised the manuscript to fit recommendations from Journal of Pediatrics except for the number of figures and tables. The current combined total of Tables and Figures is 5 [after moving table 4 into the appendix] versus a recommended number total of 4.

Since our previous submission to Pediatrics, the study listed in reference 21 (analysis of changes in DR practice at Parkland during SUPPORT and before publication of SUPPORT) has now been accepted for publication in Pediatrics. Based on Author Information on the J Peds URL, I need to include this manuscript in the submission to Journal of Pediatrics.

I attach

1. the proposed revised manuscript for J Peds;
2. the proposed letter of submission;
3. the proof of the Pediatrics paper (which according to Author Information should be attached to the submission).

Please could you review, comment and edit the first two documents.

Thanks for your collaboration and best regards,

Luc

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Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaclyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1,4</sup> Roy Heyne, MD,<sup>1</sup>  
Mambarambath Jaleel,<sup>1</sup> MD, Neil Finer, MD,<sup>5,4</sup> Waldemar A. Carlo, MD,<sup>6,5</sup>  
Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>7,6</sup> ~~Rose~~ Mary D. Higgins, MD,<sup>8,7</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: <sup>1</sup>Department of Pediatrics, UUniversity of Texas Southwestern, Dallas, TX; <sup>2</sup>Current affiliation: Pediatrix Medical Group, San Antonio, TX; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NCRFI International, Research Triangle Park, NC; <sup>4</sup>Current affiliation: The Ohio State University - Nationwide Children's Hospital; <sup>5,4</sup>Division of Neonatology, UUniversity of California, San Diego, CA; <sup>6,5</sup>Division of Neonatology, University of Alabama, Birmingham, AL; <sup>7,6</sup>Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; <sup>8,7</sup>Eunice Kennedy Shriver National Institute of Child, Health and Human Development, ICHD Neonatal Research Network, Bethesda, MD

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Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

No reprints needed

First draft: Dr LeVan wrote the first draft of the manuscript.

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Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI Endotracheal Intubation; GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Statement: No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Financial Disclosure Statement: nothing to disclose

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Conflict of Interest Statement: There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

~~nothing to disclose~~

Clinical Trial registration: NCT00063063 (GDB) and NCT00233324 (SUPPORT)

Abstract length: 248 words

Article length: 2,695 words ~~What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.~~

~~What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.~~

Revised 9/6/2013

List of Abbreviations:

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BPD, bronchopulmonary dysplasia;

CI, confidence interval;

CPAP, continuous positive airway pressure;

DR, delivery room;

ETI-Endotracheal Intubation;

GA, gestational age;

GDB, generic database;

IVH, intraventricular hemorrhage;

NEC, necrotizing enterocolitis;

NRN, Neonatal Research Network;

PDA, patent ductus arteriosus;

PMA, postmenstrual age;

ROP, retinopathy of prematurity;

RR, relative risk;

SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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### **Contributors' Statement Page**

**Jaelyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Lue P Brion:** Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

**Lisa Wrage:** Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

**Marie Gantz:** Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Myra H Wyckoff:** Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Pablo Sánchez:** Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Roy Heyne:** Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Mambarambath Jaleel:** Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Neil Finer:** Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Waldemar A. Carlo:** Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Abhik Das:** Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Barbara Stoll:** Dr. Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

**Rose Higgins:** Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abstract length: 248 words

Article length: 2,288 words

## Abstract

### Objective/Introduction

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The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

### Study Design: Methods:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

Conclusions:

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

### **Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen

saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics -included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variable:

The primary outcome variable was ETI in DR.

Additional Secondary outcome variables:

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Tertiary ~~Other secondary outcomes included~~ ~~outcomes included~~ practice such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus and feeding practice, and other outcomes (including potential confounders): BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, ~~surfactant use, DR~~ outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ~~ventilation and CPAP use,~~ patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain

differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.<sup>7-16</sup> Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176

infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose had missing inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For the most important secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 3). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast,

the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Additional unadjusted comparisons of tertiary outcome variables are shown in the appendix, table 4. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44, p=0.18).

#### **Discussion:**

Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results

of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes in centers that participate in the trial.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are being recruited. Limitation of the data to centers that stayed in the NRN during the two periods of the study allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN. Limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period. They differed from those used in SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case

of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

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This study only include a limited proportion of patients born in because we only included centers that participated in SUPPORT and remained in the NRN until the end of the study period, thereby allowing analysis of center specific changes after SUPPORT. In this

study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont

Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as

exploratory. Furthermore, the large sample size lead to the description of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity).

It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB did not include information on the rationale used for various practices used for each patient in each center. We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the small number of centers included in this

study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and prophylaxis of patent ductus arteriosus,<sup>23-25</sup> synchronized nasal intermittent positive-pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>29</sup> DR practices, including oxygen exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies. This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that institution of evidence-based changes (and associated improvement in outcomes) is that centers participating in SUPPORT might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born

at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life ~~seven~~ also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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Jaclyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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**Comment [swa1]:**

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011);

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## Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Birth weight (grams): mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965:2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808:2192 (36.9)	
Hispanic	241 (14.9)	314:2192(14.3)	
Other	46 (2.8)	105:2192 (4.8)	
Antenatal Steroids: any type	1338:1616 (82.8)	1994:2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953:1614(59.1)	1980:2229(88.8)	<.0001
Multiple birth	370 (22.9)	540:2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476:2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436:1586 (27.5)	520:2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610:2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 :2231 (5.4)	<0.0001
Maternal Antibiotics	1198:1615 (74.2)	1618:2228 (72.6)	0.28

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

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<sup>2</sup>The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary Outcome<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p-value<sup>3</sup></b>
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001

Abbreviation: RR, relative risk

<sup>1</sup> presented as n (%)

<sup>2</sup> unadjusted p-value from Chi-Square tests

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

<sup>4</sup> adjusted p-values from robust Poisson model

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**Table 3. Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Difference in Means <sup>3</sup> (95% CI)	adjusted RR <sup>3</sup> (95% CI)	Adjusted p value <sup>4</sup>
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors) <sup>4</sup>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk

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<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Appendix. Table4. Tertiary Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 1 min., n/N(%) < 3, n/N (%)	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
Apgar score, 5 min., n/N (%) < 3, n/N (%)	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19),0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age (grams)	2031 (432)	2134 (399)	<0.0001
Weight at discharge (grams)	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

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<sup>1</sup> presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of

hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

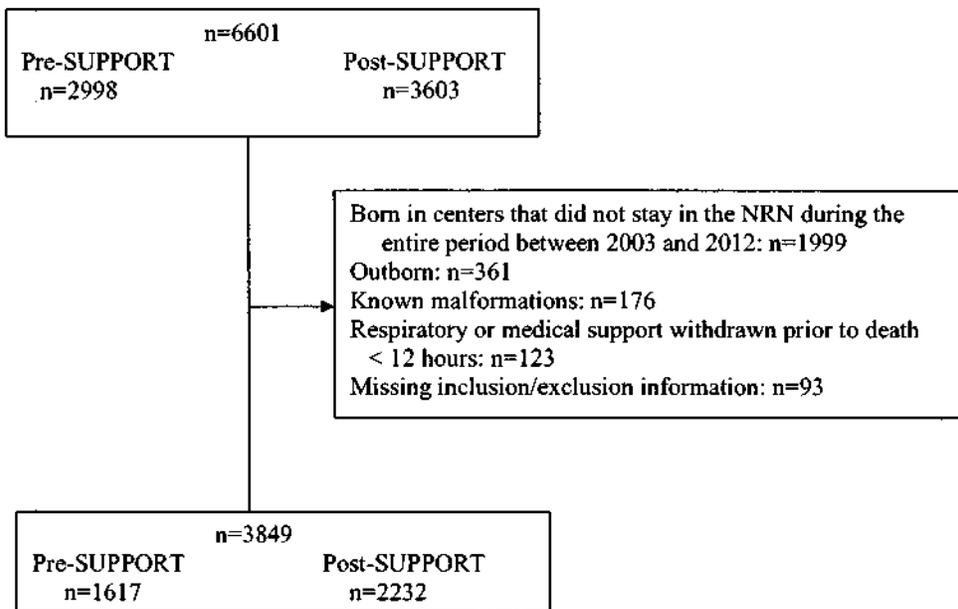
<sup>2</sup> unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup> The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup> survivors to discharge or 120 days, whichever came first, max is 120 days.

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Figure 1







Department of Pediatrics  
Division of Neonatal-Perinatal Medicine

Saturday, September 07, 2013

William F. Balistreri, MD  
The Journal of Pediatrics  
Cincinnati Children's Hospital Medical Center  
3333 Burnet Ave, MLC 3021  
Cincinnati, OH 45229-3039

Dear Dr. Balistreri:

We would like to submit an original manuscript entitled "Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" for publication in *Journal of Pediatrics*

We have previously submitted to *Pediatrics* a related manuscript, which was just accepted for publication. In that manuscript, entitled "Change in Process of Care Among Non-Enrolled Patients During and After a Randomized Trial" we had assessed changes in delivery room intubation at Parkland Memorial Hospital during SUPPORT and before publication of SUPPORT in comparison to a period before SUPPORT (January 2003-June 2005). This manuscript is described in the discussion of current manuscript (reference 21). We have uploaded the proof of this manuscript along with the current submission.

The current manuscript assesses changes in clinical practice and outcome in the NICHD Neonatal Research Network after publication of the SUPPORT Trial in comparison with those before SUPPORT. Parkland Memorial Hospital was part of the NICHD Network during the period of the study. Therefore, data from patients born at Parkland Memorial Hospital before SUPPORT (1/1/2003-12/31/2004) are included along those in 10 other NICHD Neonatal Research Network centers in the current manuscript.

The manuscript has not been and will not be submitted to any other journal while it is under consideration by *The Journal of Pediatrics*.

There is no potential conflict of interest, real or perceived. The study sponsor had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; and (4) the decision to submit the paper for publication.

Dr LeVan wrote the first draft of the manuscript.

No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Contributions of each authors are provided below:

Jaelyn M LeVan: Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

Luc P Brion: Dr. Brion conceptualized and designed the study, edited the protocol and the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

Lisa Wrage: Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

Marie Gantz: Dr. Gantz edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Myra H Wyckoff: Dr. Wyckoff edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Pablo Sánchez: Dr. Sánchez edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Roy Heyne: Dr. Heyne edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Mambarambath Jaleel: Dr. Jaleel edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Neil Finer: Dr. Finer edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Waldemar A. Carlo: Dr. Carlo edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Abhik Das: Dr. Das edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Barbara Stoll: Dr. Stoll edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

Rosemary Higgins: Dr. Higgins edited the protocol and the initial manuscript, and approved the final manuscript as submitted.

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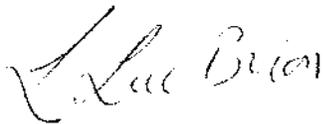
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We respectfully request to consider the attached manuscript for publication in Pediatrics. We believe this manuscript describes a study with strong design, which brings novel and significant findings that are relevant to the readership of Pediatrics.

Sincerely,



Luc P. Brion, MD

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# Change in Care Among Nonenrolled Patients During and After a Randomized Trial

Q1,2,3

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## KEY WORDS

randomized controlled trial, process of care, unblinded, preterm, endotracheal intubation, birth cohort study, non-enrolled patients

## ABBREVIATIONS

BW—birth weight  
CI—confidence interval  
CPAP—continuous positive airway pressure  
DR—delivery room  
GA—gestational age  
NNT—number needed to treat  
NRN—Neonatal Research Network  
PMH—Parkland Memorial Hospital  
RCT—randomized controlled trial  
RD—risk difference  
RR—relative risk  
SUPPORT—Surfactant, Positive Pressure, and Oxygenation Randomized Trial  
VON—Vermont Oxford Network

Dr LeVan conceptualized and designed the study, merged data from all Parkland Memorial Hospital (PMH) databases, participated in the interpretation of the data, drafted the first version of the manuscript, and critically reviewed the revisions; Drs Wyckoff, Heyne, Sanchez, Chalak, and Jaleel conceptualized and designed the study, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Ahn conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Ms Burchfield and Ms Christie collected and entered data into the databases and extracted the data for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Soll conceptualized and designed the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Badger conceptualized, designed, and conducted the statistical analyses for the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Brion conceptualized and designed the study, conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)



**WHAT'S KNOWN ON THIS SUBJECT:** Participating in a trial may affect processes of care by participating physicians; however, no study has assessed whether it affects processes of care for nonenrolled patients.



**WHAT THIS STUDY ADDS:** Participation in a trial may affect processes of care for nonenrolled patients, even when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study.

**OBJECTIVE:** Parkland Memorial Hospital (PMH) participated in Sur-Q:4 factant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded controlled trial, in which preterm neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' gestational age (GA) were randomized in the delivery room (DR) to endotracheal intubation or nasal continuous positive airway pressure. We hypothesized that DR intubation could change in nonenrolled patients at PMH and that the change would be larger than in comparable centers not participating in the trial.

**METHODS:** The PMH Cohort included eligible but nonenrolled neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks (primary) and noneligible neonates of 28 to 34<sup>6/7</sup> weeks (confirmatory). A subset (24<sup>0/7</sup>–29<sup>6/7</sup> weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in the Vermont Oxford Network (VON). We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation (during/after SUPPORT versus before SUPPORT) for PMH and for VON along with the ratio of these RRs.

**RESULTS:** In the PMH cohort ( $n = 3527$ ), the proportion of DR intubation decreased during/after SUPPORT in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96) and the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70). Compared with the RR for DR intubation in VON, the RR at PMH was smaller in the lower (ratio of RR 0.76, 95% CI 0.65–0.87) and the upper GA group (ratio of RR 0.52, 95% CI 0.39–0.68).

**CONCLUSIONS:** A center's participation in an unblinded randomized trial may affect process of care of nonenrolled patients. *Pediatrics* Q:5 2013;132:1–11

Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients.<sup>1,2</sup> Differences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.<sup>1</sup> Andersen et al showed that conducting a seeding trial (company-driven trial to entice doctors to prescribe a new drug being marketed by the company) changed some processes of care among participating physicians compared with nonparticipating physicians; however, processes of care for nonenrolled patients were not assessed.<sup>3,4</sup>

The objective of the current study was to evaluate whether a process of care of contemporaneous nonenrolled patients can change during and after recruitment to an unblinded randomized trial, when care providers participating in or familiar with the trial protocol are unaware that data on nonenrolled patients are being collected for a study. We hypothesized (1) that participation of Parkland Memorial Hospital (PMH) in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded RCT comparing processes of care, could be associated with a reduction in the proportion of delivery room (DR) intubation in nonenrolled patients, and (2) that the local practice change would be larger than in comparable centers not participating in SUPPORT.

## METHODS

### Setting

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) SUPPORT trial was a multicenter randomized 2 × 2 factorial trial in which preterm neonates of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' gestational age (GA) were randomized at birth to 2 interventions:

(1) continuous positive airway pressure (CPAP) initiated in the DR and subsequent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration, and (2) oxygen saturation targets of 85% to 89% or 91% to 95%.<sup>5,6</sup> The first intervention (CPAP versus DR intubation/surfactant) was unblinded, and its primary outcome was death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age.<sup>5</sup> PMH participated in SUPPORT from July 2005 until February 2009.

Data were compiled from 3 prospective databases, including detailed information about DR and NICU management with predetermined entry criteria and definitions: the Neonatal DR Resuscitation Registry (started in 1989), the NICU database (started in 1977), and SUPPORT registry. At PMH, all neonates <35 weeks' GA by obstetrical assessment are admitted to the NICU and included in the Resuscitation Registry and in the NICU database (unless triaged to the newborn nursery if pediatric assessment is >34 weeks' GA and the infant is otherwise well). These databases provide information on 99.8% of eligible neonates, with high interrater reliability (<1% error); most missing data points correspond to infants triaged to the newborn nursery (≤6%).

Data for an analysis cohort were abstracted by using a before–after study design during 3 consecutive epochs: (1) up to 30 months before SUPPORT initiation, (2) during SUPPORT participation, and (3) up to 15 months after trial completion. To account for secular trends in DR intubation, a subset of the PMH cohort was compared with a contemporaneous control population in the Vermont Oxford Network (VON), a voluntary collaboration of more than 900 NICUs around the world. The VON includes de-identified data by calendar year on infants with birth weight (BW)

of 501 to 1500 g. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

### Participants

The PMH cohort included neonates 24<sup>0/7</sup> to 34<sup>6/7</sup> weeks' GA born at PMH before SUPPORT (January 2003–June 2005), during SUPPORT (July 2005–February 2009), and after SUPPORT (March 2009–June 2010) until SUPPORT publication.<sup>5,6</sup> The study included (1) neonates 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' GA who were eligible for SUPPORT but not enrolled (lower GA group), and (2) noneligible neonates of 28<sup>0/7</sup> to 34<sup>6/7</sup> weeks' GA (upper GA group). The latter was used as a positive control for the lower GA group, in whom selection bias (due to exclusion of patients enrolled into SUPPORT) was possible.<sup>7,8</sup> Exclusion criteria were comfort care or major congenital anomalies known at birth, lack of patient record in the DR Resuscitation Registry or the NICU database, and enrollment in SUPPORT.

A subset of the PMH cohort, including all neonates 24<sup>0/7</sup> to 29<sup>6/7</sup> weeks' GA born in 2003 to 2004 (before SUPPORT) and 2006 to 2009 (during/after SUPPORT), was compared with inborn contemporaneous neonates born in level IIIb or IIIc North American centers participating in VON. The subset included (1) neonates 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks' GA (lower GA group), and (2) neonates of 28<sup>0/7</sup> to 29<sup>6/7</sup> weeks' GA (upper GA group). We excluded centers participating in SUPPORT or in the VON Delivery Room Management Trial,<sup>9</sup> and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies. This GA range was selected because infants in this GA range are included in the 501 to 1500 g BW range of VON. PMH was not a member of VON during the study period.

Q-6

## Comparisons of Interest

### *PMH Cohort*

The primary analysis was the adjusted relative risk (RR) of DR intubation during/after SUPPORT versus before SUPPORT in the lower GA group. The adjusted RR in the upper GA group was confirmatory and used as a positive control.

Univariate analyses in each GA group evaluated DR treatment (endotracheal intubation, positive pressure ventilation, CPAP), intubation (within the first 4 hours after admission to the NICU or during the first 24 hours of age), surfactant administration, pneumothorax, mortality to discharge from the hospital, chronic lung disease (chronic changes on chest radiograph and supplemental oxygen requirement for at least 28 days), duration of mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis (stage II or greater, modified Bell classification),<sup>10</sup> severe intraventricular hemorrhage (Papile grade III or IV),<sup>11</sup> periventricular leukomalacia, and severe retinopathy of prematurity (grade 3 or higher, international classification).<sup>12</sup>

### *Comparison With VON*

The primary analysis was the comparison of RR (adjusted for baseline variables) of DR intubation (during/after SUPPORT versus before SUPPORT) in the subset of the PMH cohort in the lower GA group with the RR of DR intubation in the contemporaneous VON cohort.

The secondary analyses were (1) the adjusted ratio of RRs for DR intubation in the upper GA group and (2) the adjusted ratio of RRs for any invasive (endotracheal tube or tracheostomy) ventilation.

## Statistical Analysis: PMH Cohort

### *Multivariate Analyses*

In each GA group, the adjusted RRs for DR intubation during/after SUPPORT versus before SUPPORT were calculated using robust Poisson regression in a generalized estimating equation model adjusted for covariates that met the  $P < .05$  criterion (backward selection). Candidate variables selected for modeling were characteristics preceding the decision of DR intubation and shown previously to associate with DR intubation.<sup>15-27</sup> To avoid collinearity with GA, BW was converted to BW z-score.<sup>28</sup> The adjusted risk difference (RD) and number needed to treat (NNT) were obtained from the adjusted RR and the proportion of DR intubation before SUPPORT. The Altman interaction test<sup>29</sup> was used to determine if the adjusted RRs for DR intubation were different between GA groups.

### *Univariate Analyses*

Univariate analyses were performed by using  $\chi^2$  tests or Fisher's exact tests for categorical variables, and Student's  $t$  tests or analyses of variance followed by Tukey test, or Kruskal-Wallis test followed by Mann-Whitney test for continuous variables. We analyzed temporal patterns of DR intubation to determine how soon after initiating SUPPORT the proportion of DR intubation changed from baseline; we selected blocks of 15 to 16 months to limit fluctuation due to sample size.

Statistical analyses were performed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance (2-tailed) was determined based on  $P < .05$ , except for multiple pairwise non-parametric comparisons, for which we used the Bonferroni adjustment.

The time interval for data abstraction was set to ascertain a sufficient number

of registered patients in the PMH cohort to detect changes in DR intubation in the lower GA subgroup using multivariate analysis. Given the ascertainment of data on 200 DR intubations, the analysis set was sufficient to conduct a multivariate analysis with up to 20 independent covariates tested as main effects, with a 2-sided  $\alpha$  of 0.05. The duration of the study was set to recruit enough patients to detect changes in DR intubation in the lower GA group by univariate analysis. The effect size was selected as a 33% RR reduction in DR intubation, a conservative estimate compared with the 47% RR reduction in DR intubation in a center in which routine DR bubble CPAP was prospectively introduced in 2000.<sup>31</sup> A sample of 97 patients before SUPPORT and during/after SUPPORT yielded 80% power to detect a reduction in DR intubation from 60% to 40% with a 2-sided  $\alpha$  of 0.05.

### *Comparison With VON*

A Poisson regression model with robust variance was used for each GA group to obtain adjusted RRs (during/after SUPPORT versus before SUPPORT) for PMH and VON along with the ratio of their RRs.<sup>30</sup> Covariates in the model were infants' GA, gender, BW, z-score, and antenatal steroids. Location (PMH and VON) and epoch (before and during/after SUPPORT) were represented by a 4-level categorical variable in the model, with the appropriate linear contrasts constructed to obtain estimates of RRs and their ratio.

## RESULTS

### **PMH Cohort**

At PMH, a total of 3821 individual patient database records were reviewed, of which 3533 were eligible and 3527 (99.8%) had records in the 3 PMH databases (Fig 1). The analysis cohort comprised 3527 records. In the lower GA group, the percentage of multiple

births was lower after SUPPORT (Table 1). In the upper GA group, exposure to antenatal steroids was more frequent after SUPPORT, maternal diabetes was more frequent during SUPPORT, and BW was greater during/after SUPPORT; other differences were clinically insignificant (Table 2).

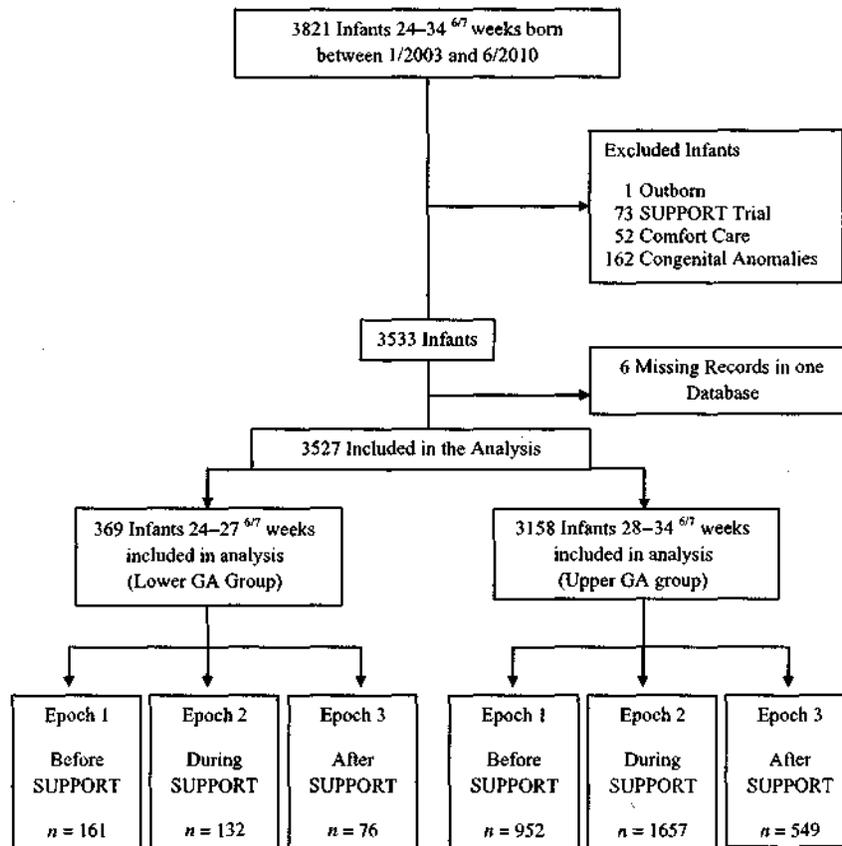
During SUPPORT, patients in the lower GA group included in the current study had a greater GA than contemporaneous patients enrolled in SUPPORT (excluded from the current study), were less likely to have been exposed to antenatal steroids, and were more likely to receive positive pressure ventilation in the DR (Appendix).

*Multivariate Analysis*

Among 3527 neonates, 649 (18%) were intubated in the DR. The proportion of DR intubation significantly decreased during/after SUPPORT versus before SUPPORT, in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96,  $P = .02$ ) and in the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70,  $P < .001$ ) (Tables 3 and 4). In the lower GA group, the proportion of DR intubation decreased from 85% before SUPPORT to 61% during/after SUPPORT (Table 5) (adjusted RD 0.21, 95% CI 0.03–0.34; NNT 5, 95% CI 3–33). In the upper GA group, the proportion decreased from 19% to 10% (Table 6) (adjusted RD 0.08, 95% CI 0.06–0.10; NNT 12, 95% CI 10–18). The decrease in DR intubation was not significantly different in the upper GA group compared with the lower GA group (adjusted ratio of RR 0.75, 95% CI 0.54–1.03).

*Univariate Analyses*

In the lower GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ( $P = .01$ ) and that of CPAP increased ( $P < .001$ ) (Table 5). Not surprisingly, the proportion of intubation in the NICU within



**FIGURE 1**  
Flow diagram at PMH.

**TABLE 1** Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Q:10  
Lower GA Group: 24<sup>0/7</sup> to 27<sup>6/7</sup> Weeks' Gestation

Characteristic <sup>a</sup>	Before SUPPORT, n = 161	During SUPPORT, n = 132	After SUPPORT, n = 76	P Value
GA, wk, mean (SD)	25.8 (1.0)	25.9 (1.1)	25.8 (1.1)	.42
BW, g, mean (SD)	858 (236)	908 (238)	874 (290)	.24
Size for age, n (%)				.52
Small for GA	19 (12)	14 (11)	10 (13)	
Large for GA	19 (12)	25 (19)	12 (16)	
Female, n (%)	74 (46)	61 (46)	36 (47)	.98
Multiple birth, n (%)	34 (21)	19 (14)	5 (7)*	.01
Antenatal steroids, n (%)	81 (50)	52 (39)	38 (50)	.14
Abruptio placentae, n (%)	6 (4)	11 (8)	4 (5)	.25
Placenta previa, n (%)	3 (2)	1 (1)	3 (4)	.25
Maternal diabetes mellitus, n (%)	6 (4)	10 (8)	8 (11)	.11
Gestational hypertension or preeclampsia, n (%)	25 (16)	28 (21)	19 (25)	.19
Clinic attendance, n (%)	146 (90)	113 (86)	67 (88)	.40

<sup>a</sup> Complete data were available for patients in the lower GA group and for GA. P values on the last column on the right are based on analyses of variance or  $\chi^2$  analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined using  $P < .025$  and P values indicated as \*  $P < .025$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

4 hours after admission increased over time ( $P = .03$ ); however, intubation within 24 hours of life decreased

during/after SUPPORT ( $P = .002$ ). The proportion of surfactant administration decreased during SUPPORT ( $P <$

**TABLE 2** Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation

Characteristic <sup>a</sup>	Before SUPPORT, n = 952	During SUPPORT, n = 1657	After SUPPORT, n = 549	P Value
GA, wk, mean (SD)	32.1 (1.8)	32.2 (1.8)	32.4 (1.8)*	.002
BW, g, mean (SD)	1824 (468)	1904 (486)*	1932 (472)*	<.001
Size for age, n (%)				.04
Small for GA	101 (11)	139 (9)	49 (9)	
Large for GA	103 (11)	239 (15)	64 (12)	
Female, n (%)	422 (46)	716 (44)	247 (46)	.64
Multiple birth, n (%)	182 (19)	333 (20)	122 (22)	.35
Use of antenatal steroids, n (%)	260 (27)	430 (26)	204 (37)**	<.001
Abruptio placentae, n (%)	23 (2)	41 (2)	11 (2)	.82
Placenta previa, n (%)	18 (2)	33 (2)	14 (3)	.66
Maternal diabetes mellitus, n (%)	88 (9)	216 (13)*	71 (13)	.01
Gestational hypertension or preeclampsia, n (%)	264 (28)	511 (30)	168 (31)	.23
Clinic attendance, n (%)	852 (90)	1530 (92)*	511 (93)*	.02

<sup>a</sup>In the upper GA group, 95% of data were available; we used the total number available as denominator. P values on the last column on the right are based on analyses of variance or  $\chi^2$  analysis (Fisher's exact tests where needed). Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined using  $P < .025$  and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

**TABLE 3** Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Lower GA Group: 24<sup>0/7</sup> to 27<sup>6/7</sup> Weeks' Gestation, n = 362

Variable	Adjusted RR <sup>a</sup>	P Value
During/after SUPPORT versus before SUPPORT <sup>b</sup>	0.76, 95% CI 0.59–0.96	.02
Positive pressure ventilation in the DR	3.61, 95% CI 2.02–6.45	<.001

For each categorical variable, the reference group is factor not present; for SUPPORT the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, and cord pH.

<sup>a</sup>Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

<sup>b</sup>Primary analysis.

**TABLE 4** Multivariate Analysis to Assess Variables Related to DR Intubation in Preterm Infants Born Between March 2003 and June 2010 at PMH: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation, n = 2742

Variable	Adjusted RR <sup>a</sup>	P Value
During/after SUPPORT versus before SUPPORT <sup>b</sup>	0.57, 95% CI 0.46–0.70	<.001
Positive pressure ventilation in the DR	6.29, 95% CI 4.73–8.37	<.001
GA (per wk)	0.74, 95% CI 0.70–0.78	<.001
Gestational hypertension or preeclampsia	0.72, 95% CI 0.56–0.92	.009
Z score of BW for GA and gender	0.91, 95% CI 0.83–1.00	.046

For each categorical variable, the reference group is factor not present; for SUPPORT, the reference group is before SUPPORT. Candidate explanatory variables found not to be significant predictors include antenatal steroid administration, gender, multiple pregnancy, general anesthesia provided to the mother at delivery, and cord pH.

<sup>a</sup>Adjusted RR estimates are derived based on Poisson regression using a generalized estimating equation model.

<sup>b</sup>Confirmatory analysis (positive controls).

.001). The proportion of pneumothoraces increased after SUPPORT ( $P = .03$ ). Most pneumothoraces occurred in neonates who were intubated in the DR.

In the upper GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT ( $P =$

.002) (Table 6). The proportion of intubation within 24 hours of life decreased during/after SUPPORT ( $P < .001$ ). The proportion of surfactant administration decreased during SUPPORT ( $P < .025$ ).

Most of the other outcomes except retinopathy of prematurity did not

change during or after SUPPORT. The percentage of DR intubation did not change during baseline in either GA group (Fig 2). In the lower GA group, the proportion of DR intubation decreased within 15 months of SUPPORT, whereas in the upper GA group, it did not significantly change until later.

### Comparison Between PMH and VON

We compared data from 576 neonates born at PMH with data from 85 118 contemporaneous neonates born in 1 of 396 North American VON centers (Table 7).

In the lower GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT at PMH (82% vs 60%; adjusted RR 0.74, 95% CI 0.64–0.86) and in VON (85% vs 84%; adjusted RR 0.98, 95% CI 0.98–0.99). The decrease was greater at PMH than in VON (adjusted ratio of RR 0.76, 95% CI 0.65–0.87). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in the VON data. The change over time was not significantly different between PMH and VON.

In the upper GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT both at PMH and in VON. The decrease was greater at PMH than in VON (adjusted ratio of RR 0.52, 95% CI 0.39–0.68). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in VON. The change over time was not significantly different between PMH and VON.

### DISCUSSION

In the current study, a change in care process (proportion of DR intubation) was observed in eligible but non-enrolled patients and in noneligible

**TABLE 5** Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: 24<sup>0/7</sup> to 27<sup>6/7</sup> Weeks' Gestation

Care Process or Outcome Variable <sup>a</sup>	Before SUPPORT, n = 161	During SUPPORT, n = 132	After SUPPORT, n = 76	P Value
Intubation in the DR, n (%)	136 (85)	81 (61)**	46 (61)**	<.001
Positive pressure ventilation in the DR, n (%)	140 (81)	106 (80)*	60 (79)*	.01
CPAP in DR, n (%)	48 (31)	74 (56)**	48 (63)**	<.001
Intubation in the NICU within the first 4 h after admission to the unit, n (%)	7 (4) <sup>b</sup>	14 (11)	10 (13)	.03
Intubation during the first 24 h of life, n (%)	141 (88)	95 (72)**	56 (73)*	.002
Surfactant, n (%)	121 (79)	78 (59)**	50 (66)	.001
Pneumothorax, n (%)	11 (7)	13 (10)	14 (18)*	.03
Death before discharge, n (%)	43 (27)	34 (26)	18 (24)	.91
Chronic lung disease, n (%)	83 (52)	61 (46)	43 (57)	.34
Total no. days intubated (endotracheal tube or tracheostomy) (n = 338); median (quartiles) <sup>c</sup>	10 (2–23)	5(1–14)	11 (2–29)	.05
Patent ductus arteriosus, n (%)	77 (48)	61 (46)	39 (51)	.78
Necrotizing enterocolitis, stage ≥2, n (%)	14 (9)	10 (8)	5 (7)	.91
Intraventricular hemorrhage, grade 3 or 4, n (%)	25 (16)	20 (15)	18 (24)	.25
Periventricular leukomalacia, n (%)	9 (6)	7 (5)	5 (7)	.92
Retinopathy of prematurity, stage ≥3, n (%)	30 (19)	12 (9)	14 (18)	.04

P values in the last column on the right are based on  $\chi^2$  analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined by using  $P < .025$ , and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

<sup>a</sup> Complete data were available for patients in the lower GA group and for GA.

<sup>b</sup> Two patients, initially intubated in the DR, were intubated again within 4 h after admission in the NICU after a trial on CPAP.

<sup>c</sup> Kruskal-Wallis tests.

**TABLE 6** Unadjusted Comparisons in Neonates Born at PMH Between March 2003 and June 2010: Upper GA Group: 28<sup>0/7</sup> to 34<sup>6/7</sup> Weeks' Gestation

Care Process or Outcome Variable <sup>a</sup>	Before SUPPORT, n = 952	During SUPPORT, n = 1657	After SUPPORT, n = 549	P Value
Intubation in the DR, n (%)	177 (19)	162 (10)**	47 (9)**	<.001
Positive pressure ventilation in the DR, n (%)	332 (36)	513 (31)*	150 (28)**	.002
CPAP in the DR, n (%)	314 (34)	588 (36)	194 (36)	.74
Intubation in the NICU within the first 4 h after admission to the unit, n (%)	43 (5)	82 (5)	28 (5)	.84
Intubation during the first 24 h of life, n (%)	220 (23)	242 (15)**	75 (14)**	<.001
Surfactant, n (%)	105 (11)	131 (8)*	50 (9)	.01
Pneumothorax, n (%)	29 (3)	40 (2)	12 (2)	.51
Death before discharge, n (%)	17 (2)	19 (1)	8 (2)	.41
Chronic lung disease, n (%)	31 (3)	40 (2)	16 (3)	.44
Total no. days intubated (endotracheal tube or tracheostomy) (n = 694); median (quartiles) <sup>b</sup>	1 (1–3)	1 (0–4)	1 (1–6)	.097
Patent ductus arteriosus, n (%)	68 (7)	106 (6)	23 (4)	.07
Necrotizing enterocolitis, stage ≥2, n (%)	17 (2)	23 (1)	12 (2)	.42
Intraventricular hemorrhage, grade 3 or 4, n (%)	8 (0.8)	7 (0.4)	5 (0.9)	.22
Periventricular leukomalacia, n (%)	3 (0.3)	13 (0.8)	4 (0.7)	.323
Retinopathy of prematurity, stage ≥3, n (%)	3 (0.3)	0 (0)	3 (0.5)	.008

P values in the last column on the right are based on  $\chi^2$  analysis (Fisher's exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using  $\chi^2$  tests, Fisher's exact tests, or Tukey tests, with significance determined by using  $P < .025$ , and P values indicated as \*  $P < .025$ , or \*\*  $P < .001$ . Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

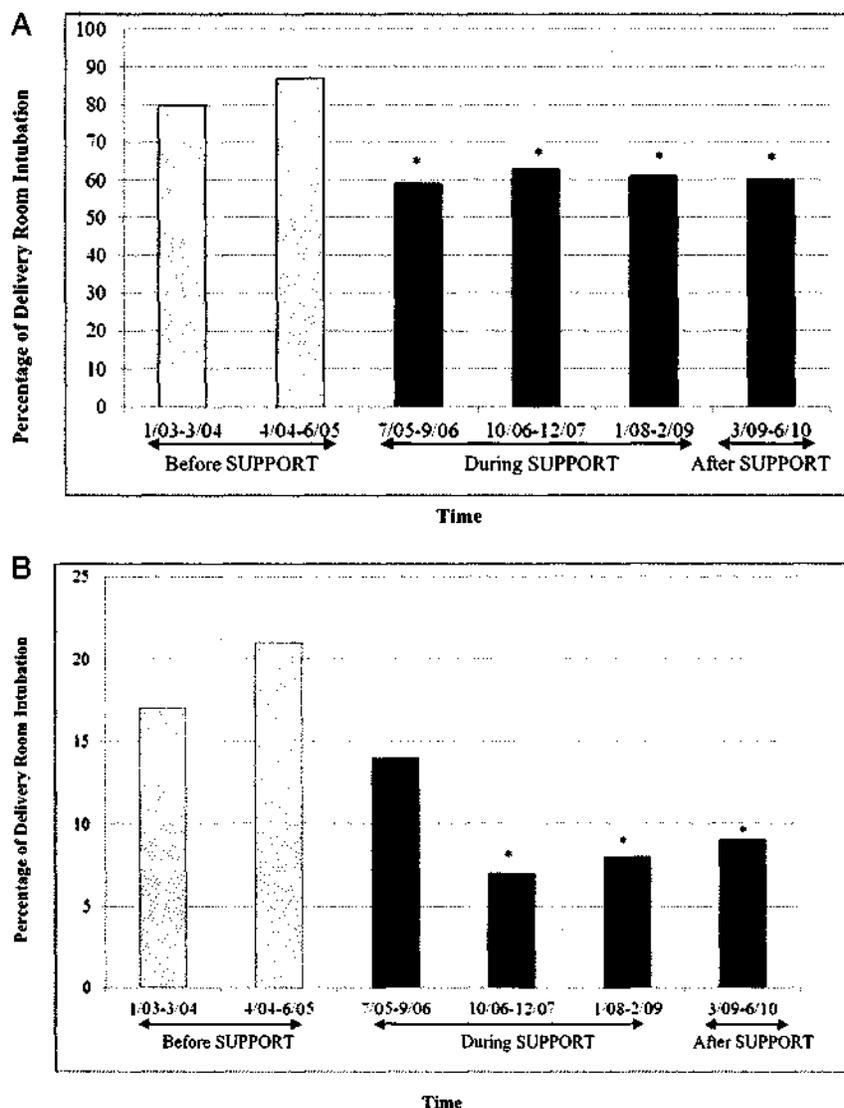
<sup>a</sup> In the upper GA group, 95% of data were available; we used the total number available as denominator.

<sup>b</sup> Kruskal-Wallis tests.

more mature patients soon after SUPPORT initiation and persisted through 16 months of posttrial evaluation. This change in practice at PMH was much larger than in other comparable centers that did not participate in any trial involving random allocation to DR intubation, suggesting that the trial participation itself influenced clinical practice well beyond the study participants.

PMH is a high-volume delivery unit with 12 000 to 15 000 deliveries per year. At PMH, the decision whether to intubate is made by resuscitation teams of practitioners who are trained in the neonatal resuscitation program. Teams for neonates with GA of 30 to 35 weeks include a nurse, a respiratory therapist, and a neonatal nurse practitioner or a senior pediatric resident. Teams for lower GA neonates also include a neonatal-perinatal fellow. Additional personnel are available for backup. The same teams provided care to all neonates, whether enrolled into SUPPORT or not. PMH did not have a policy about DR endotracheal intubation; decisions are left to team leaders according to national guidelines for neonatal resuscitation. At PMH before SUPPORT, most preterm neonates <28 weeks' GA were intubated in the DR. PMH did not participate in the NRN Feasibility Trial,<sup>15</sup> which preceded SUPPORT. At PMH, the only evident change in DR management was initiation of a resuscitation rotation for fellows in neonatal-perinatal medicine in 2005. The Neonatal Resuscitation Program mentioned the use of CPAP in the DR for preterm neonates in 2006, and included CPAP in the resuscitation algorithm in 2010<sup>31,32</sup>; however, immediate application of CPAP in the DR at PMH was not recommended for all preterm neonates <32 weeks until May 1, 2011.

The strengths of the current study include<sup>33,34</sup> large sample size; prospective validated databases thereby

**FIGURE 2**

Analysis of temporal patterns in DR intubation rates by GA group at PMH. This analysis was performed using consecutive 15- to 18-month blocks. A, Lower GA group (24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA infants): The percentages of DR intubation were not significantly different between blocks before SUPPORT ( $P = .37$ ); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into the SUPPORT ( $P < .001$ ). This change already occurred within the first 15 months of recruitment into SUPPORT. \*Indicates significant (with Bonferroni adjustment,  $P < .0125$ ) pairwise difference from baseline before starting the SUPPORT. B, Upper GA group (28<sup>0/7</sup>-34<sup>6/7</sup> weeks' GA infants): The percentage of DR intubations was not significantly different between the 2 blocks before SUPPORT ( $P = .10$ ); therefore, the overall percentage before SUPPORT was used as baseline for further comparisons. The percentage of DR intubations decreased after starting recruitment into SUPPORT ( $P < .001$ ); however, this change started to reach significance only after 15 months of recruitment into SUPPORT. \*Indicates significant (with Bonferroni adjustment,  $P < .0125$ ) pairwise difference from baseline before starting SUPPORT.

comparable centers. It is unlikely that the current study affected the proportion of DR intubation because when the first data were obtained and presented at a national meeting, the change in practice had already taken place. We did not observe a regression to the mean but instead a sustained reduction in DR intubation at PMH during/after SUPPORT. A differential Hawthorne effect was ruled out because providers were not aware of an observational study of eligible, non-enrolled patients during SUPPORT.<sup>7,8</sup> This study was limited to a single institution rather than all NRN centers participating in SUPPORT because the generic database of the NRN includes only the most immature infants; patients in the upper GA group were important in this study as positive controls who were not eligible for SUPPORT and thus not subjected to selection bias. Selection bias at PMH in the lower GA group during SUPPORT is unlikely to explain the observed decrease in DR intubation in nonenrolled patients, because respiratory distress is associated with lower exposure to antenatal steroids,<sup>35</sup> and more frequent DR positive pressure ventilation (Appendix) would be expected to increase, rather than decrease, DR intubation. The lower percentage of antenatal steroids among nonenrolled patients could have resulted because of many reasons, including not enough time before delivery.<sup>7</sup> Rich and colleagues' study showed that a significantly larger proportion of eligible infants whose mothers were not approached for consent to SUPPORT had no prenatal steroid exposure.<sup>3</sup> The frequency of antenatal corticosteroid administration at PMH is low because preeclampsia and diabetes are considered contraindications.<sup>36</sup> Multivariate analyses showed that the RR of DR intubation decreased at PMH and decreased more at PMH than in VON, even taking into account antenatal

minimizing missing data, information bias, and loss to follow-up; stratified analysis yielding internal controls (upper GA group); and multivariate comparison with contemporaneous external controls (comparable VON

centers not participating in DR trials) with a similar baseline proportion of DR intubation. Secular trends are unlikely to explain the primary results because DR intubation at PMH decreased much more than in other

**TABLE 7** Adjusted RR Estimates in Preterm Infants Born With GA 24 to 29<sup>6/7</sup> Weeks at PMH and in Comparable North American Centers in the VON Before SUPPORT (2003–2004) and During/After SUPPORT (2006–2009)

Care Process	GA Group, wk	Location	Before SUPPORT	During/After SUPPORT	Adjusted RR <sup>a</sup> During/After Versus Before SUPPORT (95% CI)	Ratio of RRs PMH Versus VON (95% CI)	P Value
Intubated in DR	24 <sup>0/7</sup> –27 <sup>6/7</sup>	PMH	105/128 (82%)	99/164 (60%)	0.745 (0.644–0.861)	0.757 (0.654–0.875)	.0002
		VON	11 728/13 726 (85.4%)	29 715/35 447 (83.8%)	0.984 (0.976–0.992)		
	28 <sup>0/7</sup> –29 <sup>6/7</sup>	PMH	51/86 (59%)	57/198 (29.0%)	0.495 (0.375–0.652)	0.516 (0.391–0.681)	
		VON	5427/10 008 (54.2%)	13 457/25 928 (51.9%)	0.959 (0.939–0.979)		
				<i>n</i> = 49 055			
Received any invasive ventilation	24 <sup>0/7</sup> –27 <sup>6/7</sup>	PMH	119/128 (93.0%)	144/164 (88.0%)	0.952 (0.886–1.023)	0.965 (0.898–1.037)	.33
		VON	13 158/13 727 (95.9%)	33 489/35 453 (94.4%)	0.986 (0.982–0.991)		
	28 <sup>0/7</sup> –29 <sup>6/7</sup>	PMH	63/86 (73.0%)	134/198 (68.0%)	0.939 (0.804–1.095)	0.988 (0.846–1.154)	
		VON	7599/10 008 (75.9%)	18 669/25 930 (72.0%)	0.950 (0.937–0.962)		
				<i>n</i> = 35 855			

<sup>a</sup> RR estimates are adjusted for infants' GA, gender, z-score for BW (computed within GA and gender), and exposure to antenatal corticosteroids by using robust Poisson regression generalized estimating equation models. Location (PMH and VON) and time period (during/after SUPPORT and before SUPPORT) were represented by a 4-level categorical variable. RRs and the ratio of RR estimates were computed based on the appropriate linear contrast of model parameters.

corticosteroid administration. We were unable to analyze bronchopulmonary dysplasia or other elements of care process examined in SUPPORT (ie, targeted ventilation strategy and oxygen saturation), which were not included in the PMH databases. In addition, target oxygen saturation values of 88% to 94%, a PMH NICU policy since May 2002,<sup>37</sup> was used for nonenrolled patients. Because the study used databases, it was not possible to perform a propensity match, or a cluster analysis of DR team members or individual providers and to obtain their rationale for deciding whether to intubate the trachea. It is possible that the change in DR intubation was related to increased availability of T-piece devices for DR resuscitation, or to training and experience with these devices and DR CPAP.

## CONCLUSIONS

A change in process of care was observed in nonenrolled patients during/after recruitment to an unblinded RCT, in the absence of changes in standard care, initiation of a protocol, or previously described trial effect. This suggests that care for patients who are not enrolled in RCTs should routinely be

monitored and audited to identify changes in practice that may either be beneficial or detrimental without the evidence from a completed trial. Further studies are needed to investigate the determinants of changes in individual decisions about care process (eg, observations of short-term outcomes versus experience with novel processes of care). A trial design in which centers are randomized to participation in RCTs could further analyze the impact of changes in care process associated with unblinded RCTs.

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The final version of the PMH cohort was a platform presentation at the Pediatric Academy Society Meeting, Boston, MA, April 28, 2012: LeVan JM, Wyckoff MH, Jaleel MA, Sanchez PJ, Ahn C, Burchfield J, Christie L, Brion LP. Impact of initiating the NICHD Neonatal Research Network SUPPORT Trial on management and out-

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(Continued from first page)

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**APPENDIX** Baseline Characteristics of Infants 24 to 27<sup>6/7</sup> Weeks' Gestation Born at PMH During SUPPORT (July 2005–February 2009)

Q:11	Characteristic	SUPPORT, n = 73, Excluded From the Current Study	NONSUPPORT, n = 132, Included in the Current Study	P Value
	GA, wk, mean (SD)	25.3 (1.0)	25.9 (1.0)	<.001
	BW, g, mean (SD)	878 (189)	907 (238)	.37
	Size for age, n (%)			.03
	Small for GA	1 (1)	14 (11)	
	Large for GA	19 (26)	25 (19)	
	Female, n (%)	29 (40)	61 (46)	.23
	Multiple birth, n (%)	12 (16)	19 (14)	.69
	Use of antenatal steroids, n (%)	49 (67)	52 (39)	<.001
	Abruptio placentae, n (%)	3 (4)	11 (8)	.39
	Placenta previa, n (%)	1 (1)	1 (1)	1.00
	Maternal diabetes, n (%)	6 (8)	10 (8)	1.00
	Gestational hypertension or preeclampsia, n (%)	15 (21)	28 (21)	1.00
	Clinic attendance, n (%)	63 (86)	113 (86)	1.00
	Positive pressure ventilation in the DR, n (%)	42 (58)	106 (80)	.001

Significance based on Fisher's exact tests or Student's *t* tests.

## AUTHOR QUERIES

### AUTHOR PLEASE ANSWER ALL QUERIES

- 1—Titles are limited to 2 lines of printed text; if your title goes beyond this limit, please reduce the length to no more than 97 characters (including spaces and punctuation). No change needed
- 2—Please verify the corresponding author's contact information. No change needed
- 3—Please verify all author names, degrees, and affiliations. Please provide degree(s) for Badger. Please provide the cities for affiliations d and e. Badger: MS; cities for c and d: Burlington; e is not used
- 4—Please confirm whether funding for this research was provided by the National Institutes of Health. If so, please provide any relevant grant information if it has not already been noted. No NIH funding
- 5—Per journal style, all abstracts must have fewer than 250 words. If your abstract extends beyond this limit, please edit as necessary (if changes are extensive, include or e-mail an electronic text file with the new abstract). No change needed
- 6—Sentence beginning "Andersen et al showed...": The end of the sentence cites references 3 (Andersen et al) and 4 (Psaty and Rennie). Change sentence to read "Andersen et al<sup>3</sup> and Psaty and Rennie<sup>4</sup> showed..."? Please do not change; the text should stay as is
- 7—Sentence beginning "Rich and colleagues' study showed that a significantly...": Please indicate which Rich reference you are citing here. Reference 7
- 8—Please include a reference for "the study by Rich and collaborators." Also, please verify that all information included in the Acknowledgments section should be there. References 7 and 8
- 9—All dots that resemble multiplication dots have been changed to decimal points throughout. Please verify. OK
- 10—Tables 1A, 1B, 2A, 2B, 3A, and 3B have been renumbered as Tables 1 to 6 per journal style. Please verify all edits to table titles and footnotes. Changes made in the the table
- 11—*P* values theoretically should never reach 1.00. Please change all 1.00 *P* values to their prerounded values.  $p=1.000$  (SPSS gives *p* value with 3 decimals)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Myles, Renate (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** Re: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 4:42:27 PM

---

Ok

Sent from my iPhone

On Sep 6, 2013, at 4:37 PM, "Bock, Robert (NIH/NICHD) [E]" <bockr@exchange.nih.gov> wrote:

Please see addition below.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 4:23 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Please review and okay:

**With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.**

(b)(5)

**Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.**

(b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 4:02 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

It might be good to (b)(5)

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:54 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

It was up to the sites – there are several kinds of surfactant available in the US.

She could (b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research  
Network  
Pregnancy and Perinatology Branch  
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6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:53 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

No, nothing about the type of surfactant used.

Rose, are there a lot of different compounds used for surfactant treatment of newborns? Or is it the same compound made in slightly different formulations by different manufacturers?

And if she wanted to find out what kind of surfactant each site used, would she have to check with the individual sites?

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:46 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, thanks.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate, let me call up the original paper and see what it says about the surfactants used. Maybe I can copy and paste it into the e-mail.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:43 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

<!--[if !supportLists]-->• <!--[endif]-->With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly

(b)(5)

<!--[if !supportLists]-->• <!--[endif]-->Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks to you both! Can you also take a look at her second and third questions at the bottom of the email?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:38 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

This looks fine  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research  
Network  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:37 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

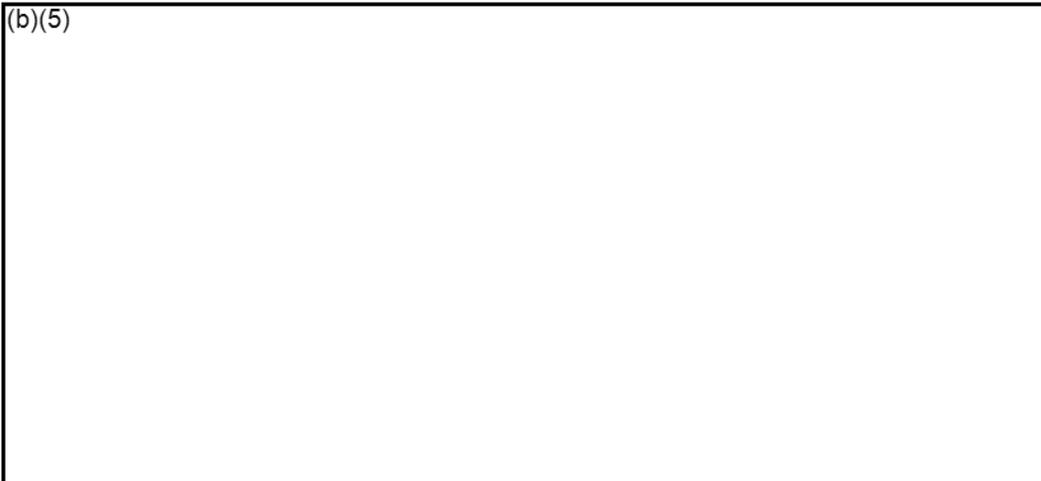
I'm going to cc Rose to save time. Rose, can you please check Renate's note below for accuracy? Renate, I made some edits to make it clear that we're talking about the Network at the time of the SUPPORT study, and not today.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 2:54 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, so would this be accurate:

(b)(5)



(b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 1:13 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

OK. It turns out NICHD was mistaken. The Data Coordinating Center at RTI did not submit a consent form because they did not see patients.

However, The DCC does have an IRB.

She may not understand that (b)(5)

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 12:37 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

More!

Sent from my BlackBerry 10 smartphone.

**From:** [mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)  
**Sent:** Friday, September 6, 2013 12:35 PM  
**To:** Skeen, Kim  
**Subject:** Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

**From:** Skeen, Kim  
**Sent:** Friday, September 6, 2013 12:27 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet.

We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Friday, September 06, 2013 11:17 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

<!--[if !supportLists]-->• <!--[endif]-->For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?

<!--[if !supportLists]-->◦ <!--[endif]-->We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).

<!--[if !supportLists]-->◦ <!--[endif]-->Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)

<!--[if !supportLists]-->• <!--[endif]-->With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

<!--[if !supportLists]-->• <!--[endif]-->Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

<!--[if !supportLists]-->1. <!--[endif]-->**How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

<!--[if !supportLists]-->2. <!--[endif]-->**What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

<!--[if !supportLists]-->3. <!--[endif]-->**How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [myles@mail.nih.gov](mailto:myles@mail.nih.gov)  
Web: <http://www.nih.gov>

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---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

<!--[if !supportLists]-->• <!--[endif]-->NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.  
<!--[if !supportLists]-->• <!--[endif]-->RTI's NIH funding information is publicly available from NIH.  
<!--[if !supportLists]-->• <!--[endif]-->The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

---

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from

NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
410-591-9567 cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 11:24 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami

**Subject: RE: CBS News is trying to reach you**

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

<!--[if !supportLists]-->• <!--[endif]-->We are aware of concerns voiced about the informed consent document regarding this particular study.

<!--[if !supportLists]-->• <!--[endif]-->RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.

<!--[if !supportLists]-->• <!--[endif]-->As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(6) cell  
skeenk@cbsnews.com

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Smith, Nancy M <Nancy.M.Smith@uth.tmc.edu>  
**Sent:** Friday, September 06, 2013 4:14 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** OHRP statement  
**Attachments:** Misconceptions\_about\_the\_SUPPORT\_Trial1111.docx

Dr. Guttmacher,  
Dr. Jon Tyson asked that I forward you a copy of the statement that he submitted on the ORHP website under comments today.  
Thanks,  
Michelle

N. Michelle Smith  
Sr. Executive Assistant to Jon E. Tyson, MD, MPH

 **The University of Texas**  
Health Science Center at Houston | **Medical School**

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[Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu)

## **Misconceptions about the SUPPORT Trial**

As both investigators in the SUPPORT trial and attendees at the OHRP meeting August 28, 2013, we found that multiple speakers at the meeting had fundamental misconceptions about this trial as addressed below. It is important to address these misconceptions partly because they may cause not only SUPPORT but other major comparative effectiveness trials in patients of any age to be misinterpreted by OHRP, clinicians, ethicists, the lay public, or others who read the reports from this meeting.

### **Misconception 1. Infants died as a result of participating in the study.**

This has been assumed because the lower oxygen saturation group had a significantly higher mortality than the higher saturation group. However, the infants in both study groups had a lower mortality (19.9%; 16.2%) than those not enrolled (24.1%) and historical controls (23.1%). When risk adjusted for characteristics of the non-enrolled infants, those in the study were still at no higher risk of death.<sup>1</sup> These results are not surprising given the systematic reviews indicating that participants in randomized trials have no worse outcomes and tend toward better outcomes than otherwise similar patients not enrolled in trials.<sup>2</sup> In some trials, patient risk may be reduced by the investigators' efforts to most effectively provide the therapies under investigation, to optimize the patient's supportive care and clinical monitoring, and to minimize and more quickly identify and address treatment hazards or disease complications than would occur in clinical practice. In the SUPPORT trial, it is entirely possible that oxygen administration was more carefully adjusted among infants in the trial than among infants given usual care.

### **Misconception 2. Participation in SUPPORT denied participating infants the advantage of individualized oxygen saturation goals. Had SUPPORT been properly designed, it would have included a 3<sup>rd</sup> group who received the usual care that otherwise would have been given.**

The above data do not support these views, and there are no studies showing that caregivers somehow know how to individualize the oxygen saturation goal for different extremely premature infants to improve their outcomes. Without studies like SUPPORT, there simply has not been anything close to the evidence base needed to guide treatment decisions.

Perhaps some critics of SUPPORT unfamiliar with neonatal care have mistakenly inferred that infants in the same saturation group received the same inspired oxygen concentration regardless of differences or variation in their condition. The inspired oxygen concentration for each infant was highly individualized in an effort to maximize the time that the oxygen saturation was within the goal range. The caregivers for unstable infants with recurrent apneic episodes, pulmonary artery hypertension, pneumonia, aspiration, pneumothorax, or other problems adjusted the inspired oxygen concentration many times within each day. As an example, more than 600 individual oxygen adjustments were documented to maintain a single infant within the range of the study parameters during a feasibility pilot in one center.

Adding a third treatment group with a saturation goal of 85-95% spanning the goals for the other two groups would be expected to produce outcomes intermediate between these groups. Most importantly, the increased number of infants required would have delayed by more than two years when the study was completed and when the higher mortality with the lower saturation goal was first identified and reported to neonatologists making treatment decisions for extremely premature infants around the world.

### **Misconception 3. The primary outcome used to compare the two oxygen saturation groups—death or severe ROP—indicates the investigators believed that mortality would be affected.**

In clinical trials involving high-risk patients, patients often die without surviving long enough to experience the outcome a therapy is hypothesized to decrease. Even when no effect of the therapy on death is hypothesized or plausible, it is often appropriate to include death as a competing outcome in the primary outcome. Randomized trials are considered to be the gold standard for testing therapies because randomization

minimizes the likelihood of important baseline differences between treatment groups in known or unknown factors that affect outcome independent of the treatment. Excluding patients after randomization, particularly ones who die, violates the intention-to-treat principle for analysis of randomized trials and can cause baseline differences between the groups as analyzed that result in erroneous conclusions. The trial conclusions should be consistent with the findings for the predefined primary outcome. A primary outcome that does not include death is particularly problematic if there are unexpected differences in death, as in a trial of intensive glucose lowering when mortality was unexpectedly increased even though myocardial infarction was reduced.<sup>3</sup> As for other Network trials in which the primary outcome often includes death as a competing outcome, it should not be assumed that the investigators believed that mortality would be affected.

**Misconception 4. The SUPPORT investigators knew--or should have known--that mortality would be higher with an oxygen saturation goal of 85-89% than an oxygen saturation goal of 90-95% percent.**

This misconception appears to be inferred from studies performed in the 1950s, three decades before oxygen saturation monitoring became available in neonatal units. In these studies, no more than 40-50% oxygen was administered<sup>4,5</sup> even to blue and gasping infants whose oxygen saturation values were undoubtedly very far below 85%. These studies are irrelevant to current care in which oxygen saturation is monitored continuously, and 100% oxygen and mechanical ventilation are provided if necessary to meet the saturation goal.

It is clear that the mortality of high-risk infants can be increased by administering too much oxygen<sup>6</sup> as well as too little oxygen. Even brief administration of 100% oxygen to term newborns during resuscitation can increase oxidant stress and cause worse outcomes than with resuscitation with room air.<sup>6</sup> Additional evidence indicates that because of their developmental deficiency in antioxidant enzymes, premature infants are less able than term infants to tolerate exposure to high concentrations of oxygen. In two large multicenter trials<sup>7,8</sup> mortality was somewhat higher with oxygen saturations in the high 90s than oxygen saturations in the low 90s. Thus, neonatologists questioned whether an oxygen saturation of 90-95% was too high for extremely premature infants whose oxygen saturation would have been ~50% had they remained in utero.

SUPPORT was performed to better define the saturation goals that would optimize short and long-term outcomes. The best contemporary evidence suggested that saturation goals of 85-89% and perhaps goals as low as 70%, would be safe,<sup>9,10</sup> would not increase<sup>9</sup> and might decrease mortality<sup>6,7,8,10</sup> (and neurodevelopmental impairment), and supported the investigators' primary hypothesis that the lower saturation goal would increase survival without severe retinopathy of premature (ROP).

As is standard in randomized trials, including all Neonatal Research Network trials, the measures to protect patients from unanticipated hazards included formal monitoring of the interim results by an independent Data Safety and Monitoring Committee. This committee used carefully predefined stopping rules in reviewing the interim data for death, ROP, and other major outcomes on three different occasions during SUPPORT. Even with such monitoring by an expert committee, a better overall outcome for the higher saturation group was not sufficiently predictable to stop the trial early.

A significant difference in mortality was not identified in all recently completed similar trials,<sup>11</sup> and the mortality difference in SUPPORT was large enough to be statistically significant ( $p = 0.046$ ) but not highly statistically significant. While we believe that mortality was truly increased with a saturation goal of 85-89% during SUPPORT, this increase should not be viewed as predictable or inevitable.

**Misconception 5. Death should have been specified on the consent form as a reasonably foreseeable risk for the 85-89% saturation group to better inform the parents.**

As noted by Tyson et al in the material previously submitted for this OHRP meeting, reasonably foreseeable potential risks include a) biologically plausible treatment hazards that have been poorly assessed in clinical

studies, and b) hazards that have been evaluated in a systematic review of relevant clinical trials or in the absence of such a review, in one or more clinical trials or well performed cohort studies and found to marginally or significantly associated with the treatment ( $p \leq 0.10$ ). In accordance with the principles of evidence-based medicine, investigators should not be required to list on a consent form all possible hazards or hazards that are not close to significant ( $p > 0.10$ ) in these prior studies. Deeming such potential hazards as "reasonably foreseeable" would require investigators to list almost any hazard that that could be considered minimally plausible despite evidence to the contrary. This approach might more often mislead than inform potential research participants or their surrogates.

Because the relevant clinical trials and cohort studies referenced above did not provide any evidence that mortality would be increased in the lower saturation group, this result should not be considered reasonably foreseeable. Such evidence supports the approval of the consent forms by the IRB in each of the 20 participating centers. If the possibility of increased risk of death were to be noted on the consent form, the best available evidence would indicate that it would need to be noted as risks for both the higher and lower saturation groups. We doubt that this approach would have made parents better informed or more satisfied. As in SUPPORT, an unavoidable problem with informed consent in comparative effectiveness trials is that the information needed to make a truly informed decision is unknown and that surprises are sometimes unavoidable. Otherwise the trial would not have been needed.

Some speakers argued that the consent form used in the similar New Zealand trial would have been preferable to the forms used in SUPPORT. While carefully written, the New Zealand form did not note the possibility of increased mortality in the higher as well as the lower saturation groups. The preference for this form can be viewed as an example of "Monday morning quarterbacking" based on the final results rather than on the best data available prior to the study.

While almost any approach to seeking consent may potentially be improved, critics of SUPPORT would likely agree that the parents of infants in the study systematically received more information about the risks and benefits of different saturation goals than have the parents of the vast majority of infants treated in neonatal units worldwide since oxygen saturation monitoring was introduced in the 1980s. In the absence of trials like SUPPORT to help determine the most desirable oxygen saturation goals, these infants have received whatever saturation goals their physicians happened to select, including saturation goals equal to or lower than the lower saturation goal in SUPPORT.<sup>7</sup>

To better inform all patients or their surrogates, not just the small proportion approached for research, and to promote the evaluation and identification of ineffective or harmful therapies before they are widely used, why shouldn't the discussion be broadened to address the desirable level of risk disclosure for unproven therapies whenever they are used?

**Moving forward from here.** There is a pressing need to develop better approaches to risk identification and disclosure for use of unproven therapies in comparative effectiveness research, clinical practice, and quality improvement activities in promoting a learning health care system.<sup>12,13</sup> This need requires further study of such issues as the wants, needs, and comprehension of patients (or their surrogates) in emergent as well as in routine circumstances; the effects of differing approaches to risk disclosure (including nocebo effects<sup>14</sup>); and factors that can augment the validity of informed consent including greater parental involvement in this process. It is difficult to see how any ethical principles including respect for persons, beneficence, or justice justify a systematically different level of risk disclosure and consent in clinical practice and clinical research for patients receiving the same unproven treatment method. There also seem to be no data to indicate that well informed patients support this double standard. We believe such issues warrant much more consideration, discussion, and formal study than the misconceptions noted above.

**Authors (in alphabetical order): Carl D'Angio, MD, Neil Finer, MD, Nancy Newman, RN, Brenda Poindexter, MD, Jon Tyson, MD, MPH, and Michele Walsh, MD, MS**

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## REFERENCES

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- <sup>2</sup> Vist GE, Bryant D, Somerville L, Birmingham T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev*. 2008:MR000009.
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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Myles, Renate \(NIH/OD\) \[E\]](#)  
**Cc:** [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 4:03:49 PM

---

Agree!!

Rosemary D. Higgins, MD  
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---

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, September 06, 2013 4:02 PM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Myles, Renate \(NIH/OD\) \[E\]](#)  
**Cc:** [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI

It might be good to (b)(5)

(b)(5)

---

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, September 06, 2013 3:54 PM  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Myles, Renate \(NIH/OD\) \[E\]](#)  
**Cc:** [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI

It was up to the sites – there are several kinds of surfactant available in the US.

She could (b)(5)

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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:53 PM  
**To:** Myles, Renate (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

No, nothing about the type of surfactant used.

Rose, are there a lot of different compounds used for surfactant treatment of newborns? Or is it the same compound made in slightly different formulations by different manufacturers?

And if she wanted to find out what kind of surfactant each site used, would she have to check with the individual sites?

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:46 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, thanks.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate, let me call up the original paper and see what it says about the surfactants used. Maybe I can copy and paste it into the e-mail.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:43 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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301-496-3790 (FAX)  
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---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks to you both! Can you also take a look at her second and third questions at the bottom of the email?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:38 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

This looks fine  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:37 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I'm going to cc Rose to save time. Rose, can you please check Renate's note below for accuracy?  
Renate, I made some edits to make it clear that we're talking about the Network at the time of the

SUPPORT study, and not today.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 2:54 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, so would this be accurate:

(b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 1:13 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

OK. It turns out NICHD was mistaken. The Data Coordinating Center at RTI did not submit a consent form because they did not see patients.

However, The DCC does have an IRB.

She may not understand that (b)(5)

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 12:37 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

More!

Sent from my BlackBerry 10 smartphone.

---

**From:** [mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)  
**Sent:** Friday, September 6, 2013 12:35 PM  
**To:** Skeen, Kim  
**Subject:** Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

---

**From:** Skeen, Kim  
**Sent:** Friday, September 6, 2013 12:27 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Friday, September 06, 2013 11:17 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?
  - We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).
  - Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
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(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

**2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:

<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

**3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**

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Tel: 301-435-3638  
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Web: <http://www.nih.gov>

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**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:bistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell

[skeen@cbsnews.com](mailto:skeen@cbsnews.com)

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 11:24 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 3:53:13 PM

---

It is not in the paper. In the Manual of Procedures, it states:

### **5.3.4 Surfactant Type**

All centers are asked to follow current unit practice in determining the type of surfactant utilized and manufacturers' recommendations for re-dosing intervals

It was left up to the individual centers

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:46 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, thanks.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Renate, let me call up the original paper and see what it says about the surfactants used. Maybe I can copy and paste it into the e-mail.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:43 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks to you both! Can you also take a look at her second and third questions at the bottom of the email?

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:38 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

This looks fine  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:37 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I'm going to cc Rose to save time. Rose, can you please check Renate's note below for accuracy?  
Renate, I made some edits to make it clear that we're talking about the Network at the time of the SUPPORT study, and not today.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 2:54 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, so would this be accurate:

(b)(5)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 1:13 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

OK. It turns out NICHD was mistaken. The Data Coordinating Center at RTI did not submit a consent form because they did not see patients.

However, The DCC does have an IRB.

She may not understand that (b)(5)

(b)(5)

She may (b)(5)

(b)(5)

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 12:37 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

More!

Sent from my BlackBerry 10 smartphone.

---

**From:** mylesr@od.nih.gov  
**Sent:** Friday, September 6, 2013 12:35 PM  
**To:** Skeen, Kim  
**Subject:** Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

---

**From:** Skeen, Kim  
**Sent:** Friday, September 6, 2013 12:27 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [mailto:mylesr@od.nih.gov]  
**Sent:** Friday, September 06, 2013 11:17 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

---

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?
  - We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).
  - Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
skeenk@cbsnews.com

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

3. **How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [myles@mail.nih.gov](mailto:myles@mail.nih.gov)  
Web: <http://www.nih.gov>

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**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim

Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

---

**From:** Skeen, Kim [<mailto:Skeenk@cbsnews.com>]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeen@cbsnews.com](mailto:skeen@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

**Sent:** Wednesday, September 04, 2013 11:24 AM

**To:** Skeen, Kim

**Cc:** Spangenberg, Kami

**Subject:** RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

[RTI International's Role in the NICHD Neonatal Network SUPPORT Study](#)

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,

Lisa

Lisa Bistreich-Wolfe

Media Relations Manager

RTI International

919.316.3596

[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim [[SMTP:SKEENK@CBSNEWS.COM](mailto:SKEENK@CBSNEWS.COM)]

**Sent:** Tuesday, September 03, 2013 4:55:51 PM

**To:** News

**Subject:** CBS News is trying to reach you

**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 3:44:36 PM

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 3:44 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Thanks, Rose. Do we need the highlighted section below? Might be (b)(5)

(b)(5)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:43 PM  
**To:** Myles, Renate (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.

(b)(5)

- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

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---

**From:** Myles, Renate (NIH/OD) [E]

**Sent:** Friday, September 06, 2013 3:39 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]

**Subject:** RE: CBS News questions regarding RTI

Thanks to you both! Can you also take a look at her second and third questions at the bottom of the email?

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

**Sent:** Friday, September 06, 2013 3:38 PM

**To:** Bock, Robert (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]

**Subject:** RE: CBS News questions regarding RTI

This looks fine

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** Bock, Robert (NIH/NICHD) [E]

**Sent:** Friday, September 06, 2013 3:37 PM

**To:** Myles, Renate (NIH/OD) [E]

**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: CBS News questions regarding RTI

I'm going to cc Rose to save time. Rose, can you please check Renate's note below for accuracy?

Renate, I made some edits to make it clear that we're talking about the Network at the time of the SUPPORT study, and not today.

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**From:** Myles, Renate (NIH/OD) [E]

**Sent:** Friday, September 06, 2013 2:54 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Okay, so would this be accurate:

(b)(5)

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**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

OK. It turns out NICHD was mistaken. The Data Coordinating Center at RTI did not submit a consent form because they did not see patients.

However, The DCC does have an IRB.

She may not understand that (b)(5)

(b)(5)

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 12:37 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

More!

Sent from my BlackBerry 10 smartphone.

**From:** [mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)  
**Sent:** Friday, September 6, 2013 12:35 PM  
**To:** Skeen, Kim  
**Subject:** Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

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Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**Sent:** Friday, September 06, 2013 11:17 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

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I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,

Renate

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?
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Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

1. **How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

2. **What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

**3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

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The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 301-435-3638  
Email: [myles@mail.nih.gov](mailto:myles@mail.nih.gov)  
Web: <http://www.nih.gov>

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---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]

**Sent:** Thursday, September 05, 2013 11:33 AM

**To:** Skeen, Kim

**Cc:** Spangenberg, Kami

**Subject:** RE: CBS News is trying to reach you

Kim,

Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]

**Sent:** Thursday, September 05, 2013 11:23 AM

**To:** Bistreich-Wolfe, Lisa

**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Skeen, Kim

**Sent:** Wednesday, September 04, 2013 3:09 PM

**To:** 'Bistreich-Wolfe, Lisa'

**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes

exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

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**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

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Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 11:24 AM

**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(6) cell  
skeenk@cbsnews.com

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 3:43:27 PM

---

Just sent -

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 3:43 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI  
**Importance:** High

**Hi again, Rose. Please see the two questions highlighted below.**

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?
  - We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).
  - Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
- Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office

(b)(6) ell

[skreenk@cbsnews.com](mailto:skreenk@cbsnews.com)

- 1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

- 2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:  
<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

- 3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**  
Acting Chief  
News Media Branch  
National Institutes of Health  
Tel: 801-435-3638  
Email: [mylesr@mail.nih.gov](mailto:mylesr@mail.nih.gov)  
Web: <http://www.nih.gov>

**NIH . . . Turning Discovery Into Health**

**Celebration of Science at NIH:** watch how medical research saves lives and improves health

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

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[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]; (kzaterka@rti.org); (mcunningham@rti.org)  
**Subject:** FW: 2014 PAS abstract resubmission  
**Date:** Friday, September 06, 2013 3:04:30 PM  
**Attachments:** 2014 PAS abstract proposal unmet need.docx  
PAS Abstract Responses to Feedback - Preskitt 2014.docx

---

Can we send an email Monday after the items are posted on the private website to the various subcommittees?

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Julie K Preskitt [mailto:[preskitt@uab.edu](mailto:preskitt@uab.edu)]  
**Sent:** Friday, September 06, 2013 3:02 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; [newman@rti.org](mailto:newman@rti.org); Vivien A Phillips; Ada Myriam Peralta-Carcelen; Waldemar A Carlo  
**Subject:** 2014 PAS abstract resubmission

Good afternoon,

Thank you for the opportunity to revise our abstract proposal, "Unmet Need for Health and Related Services in Extremely Preterm Infants at 18-22 Months of Age." Attached please find our point-by-point response to reviewer feedback and the revised proposal. We have highlighted sections of the narrative that specifically relate to our responses and modifications.

We appreciate your attention, Jamie, in assuring that this revised version is the one uploaded or forwarded to reviewers for further consideration. Thank you in advance.

Julie Preskitt, MSOT, MPH, PhD  
Assistant Professor  
Health Care Organization and Policy  
School of Public Health  
University of Alabama at Birmingham  
RPHB 330  
1720 2nd Ave. S  
Birmingham AL 35294

W: 205-934-8757  
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E: [preskitt@uab.edu](mailto:preskitt@uab.edu)

## **Unmet Need for Health and Related Services in Extremely Preterm Infants at 18-22 Months of Age**

### **Abstract/synopsis**

We propose to study the level of unmet need for health and related services recommended for extremely preterm (EP) infants in the NICHD Neonatal Research Network (NRN) Follow-up Study by analyzing caregiver responses to specific questions about special child services at the 18 to 22 month corrected age (CA) follow-up visit. We will analyze received or receiving services and services recommended by a medical professional but not received by EP infants (less than 27 weeks) to determine baseline levels of unmet need overall and for each service type. We will also develop analytical models to determine whether some subgroups of children have different levels of unmet need compared to others and identify characteristics that may be associated with unmet need in this population.

### **Statement of Problem/Rationale/Justification**

Though by definition, children with special health care needs (CSHCN) have conditions that require them to use health and related services at levels that are above those for typical peers (1), the target population for this project – infants who were born extremely preterm (less than 27 weeks gestation), subsequently referred to as EP – are at a significant risk for poor health, developmental, educational, and employment outcomes (2-8). Despite the availability of information on the unmet health and related service needs for CSHCN in general and for a few subgroups (9-14), limited information is available about this issue for children who were born EP. This is a group that may be particularly vulnerable to negative health, developmental, and financial consequences of delayed care or forgone care, making them a population for whom increased knowledge about need and unmet need is a critical next step in developing more comprehensive service delivery systems.

### **Hypotheses**

- 1| EP infants in the NRN Follow-up Study have overall rates of unmet need for health and related services of at least 36.5% at 18 to 22 months.
2. Certain subgroups of EP infants in the NRN Follow-up Study have higher rates of unmet need for health and related services (overall and for specific services) at 18 to 22 months than do others.

### **Specific Aims**

- 1| To determine overall and service-specific levels of unmet need for health and related services recommended by medical professionals for EP infants at 18-22 months of age.

Version date: April, 2013

Revised: September, 2013

2. To identify characteristics (demographic or condition-specific) that are associated with unmet need for health and related services in EP infants at 18-22 months of age.

### Background/Previous studies

Infants who were extremely preterm or extremely low birthweight fit within the broad federal definition of children with special health care needs (CSHCN) based on risk, diagnosed conditions, and service usage. Children who were preterm and/or low birth weight are at increased risk for poor health, developmental, cognitive, and psychosocial/behavioral outcomes (2-8). Typically, the smaller and earlier the infant, the greater the risk for these negative health, social, educational, and developmental outcomes (2-5, 8).

Related to unmet need for CSHCN in general, 19.8% of caregivers of CSHCN ages 0-5 years reported that their child had experienced one or more unmet needs for health and related services over the year prior to the survey (9). Other studies have examined service use and unmet need in CSHCN, finding wide variation based on type of service and specific demographic and condition variables (10-14).

Little is known specifically about health and related service utilization and unmet need in children who were extremely preterm and/or extremely low birthweight. Hintz et. al. (15) included children followed in the NRN who were born at less than 28 weeks gestation and with birthweight less than 1000 grams. Focusing on a group of infants born January 1, 1997 to December 31, 2000, the authors found 36.5% of caregivers reported an unmet need for one or more health services, with a range of unmet need levels from 3.6% to 24.0% depending upon the service. Due to the nature of the standardized question related to service use and need that was a part of the NICHD NRN Follow-up Study at that time, Hintz and colleagues focused on perceived need for services based on the caregiver's perspective. Although the revised question is still answered by the caregiver, the new version now adds the clarification that frames the question around services that were recommended by a medical professional but not received.

Though we have limited information on unmet needs for health and related services among CSHCN in general and for a few specific subgroups, there is a paucity of recent literature focusing specifically on this issue for EP infants. Therefore, our proposed study will focus exclusively on EP infants – a group that may be more vulnerable to negative outcomes related to delayed care and unmet need. We will focus on infants who were born at less than 27 weeks gestation and who were seen for follow up visits at 18-22 months between April 1, 2011 and July 31, 2013. We will not include birthweight criteria to allow an exclusive focus on extreme prematurity and to avoid any potential confounding related to the inclusion of older, yet small for gestational age infants.

Results will provide more recent data not only about unmet need in this population in general (overall and by specific service), but also subsets that may experience the greatest challenges to obtaining services recommended by a medical professional for health and related services. In addition we will be able to compare unmet needs with those of the earlier study from Hintz et. al. (15) publication. Our findings will have important policy and practice implications related to the system of care for this vulnerable population. If certain services or groups of services prove to be more difficult to obtain in general or for specific subgroups of infants, then efforts can be made by policy-makers,

Version date: April, 2013

Revised: September, 2013

advocates, practitioners, and insurers to target these gaps. This will also provide important information for consideration in designing, implementing, and advocating for service delivery models and benefit packages, including establishing the details of essential health benefits contained in the Affordable Care Act and in the broader scope of health reform.

### Methods/Procedures

- Description of study design (masked, randomized, etc.)

As part of the NICHD NRN Follow-up Study, data on recommendations and receipt of specific health and related services have been collected at 18 to 22 months (CA) in all EP infants since 1993. Study coordinators have recorded caregiver responses to a multi-item question related to various health and related services that may be utilized by this population. Given that the standardized question changed slightly in April 2011 to add the clarification of services recommended by a medical professional, we propose a secondary data analysis of retrospective data gathered from caregivers of all EP infants (less than 27 weeks) in the NICHD NRN Follow-up Study who were evaluated at 18 to 22 months (CA) from April 1, 2011 – July 31, 2013.

- Definition of study population

The proposed study population includes all participants from all sites of the NICHD NRN Follow-Up Study who were born at less than 27 weeks gestation and who completed a follow-up visit at 18-22 months between April 1, 2011 and July 31, 2013.

- Description of study intervention

The proposed study will access selected secondary data gathered as a part of the NICHD NRN Follow-Up Study. All data are collected through a caregiver interview, with all the known potential biases related to recall and subjectivity. Our dependent variable will utilize data from question 1 of section E, "Special Child Services" (see Appendix 1). The variable will be developed and coded as detailed in Appendix 2. Independent, predictor variables will be included as listed and described in Appendix 3.

We will first create a demographic profile of the sample, including information on health and related service utilization (See Appendix 4, Table 1). Next, we will develop a profile of services received/receiving and recommended but not received (unmet need) for EP infants at 18-22 months (See Appendix 4, Table 2). Finally, we will create dichotomous dependent variables of unmet need (service non-receipt) overall and for each individual service/category of services, assuming a large enough sample size. We will then develop logistic regression models including demographic and condition-specific information gathered as a part of the study protocol. Given anticipated collinearity among predictor variables, we plan to develop 3 sets of models (See Appendix 4, Table 3): 1) Demographics + neurodevelopmental impairment (see definition as presented in Appendix 3), 2) Demographics + child neonatal history, and 3) Demographics and child current condition.

- Precise definition of primary/secondary outcomes

Version date: April, 2013  
Revised: September, 2013

As previously discussed, the proposed project is a secondary data analysis related primarily to unmet need and the characteristics associated with unmet need. We will also include service utilization as a part of our reported results. Although our inclusion criteria will begin with infants born one week earlier than Hintz et. al (15) and with no birthweight limit, our findings from infants born more recently will be comparable and will serve to begin a discussion of how the system of care for this population of EP infants has changed (or not) over time. The primary outcomes address the specific aims and hypotheses listed above. We plan to work with the assigned biostatistician to analyze data using univariate, bivariate, and multivariate (logistic regression) methods. Primary outcomes include:

1. Description of more recent levels of unmet need for health and related services as experienced by infants born at less than 27 weeks gestation
2. Identification of specific services that are more difficult to obtain than are others (more likely to be reported as an unmet need)
3. Identification of demographic and condition characteristics that are associated with unmet need (overall and for specific services/groups of services)

We anticipate developing tables for results as follows:

- Table 1: Demographic description of population
  - Table 2: Profile of services recommended by a medical professional for this population stratified by received or receiving and recommended but not received
  - Table 3: Odds ratios from logistic regression models based on selected demographic and condition-specific characteristics and unmet need (non-receipt of services)
- Sample size estimate with some statistical support based upon primary outcome

Preliminary examination of recent data suggests that approximately 769 children were seen for their 18-22 month follow-up visit between April 1, 2011 and February 28, 2013. Assuming similar follow-up rates across our entire date range of inclusion (through July 31, 2013), we anticipate about 936 children to be included in the sample. Although we are not testing specific hypotheses related to subgroups, power can be estimated for the hypothesis related to overall level of unmet need. Using the estimate of 36.5% of caregivers reporting one or more unmet need (from Hintz et. al.), alpha set at 0.05, and a standard deviation of 5%, we would need a sample size of 738 to reach power of 0.80.

**UPDATE:** A query of the Follow-Up Study database (conducted 8/29/13) shows 1488 infants have completed Follow Up Study Status Forms (NF10). This includes infants who were lost to follow up and those who died post discharge. Assuming an 84% follow up rate, this would yield a sample size of about 1250 infants. We have therefore exceeded

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Revised: September, 2013

**the estimated sample size and statistical power is above 95% to estimate unmet need within +/- 5% of the Hintz estimate (36.5%).**

- **Available population/compatibility with other ongoing protocols**

**These data of interest are gathered as a part of the standard follow-up visit at 18-22 months. There will be no conflict with ongoing protocols and no additional recruitment or data gathering is required. The proposed project is a secondary data analysis.**

- **Estimate of projected recruitment time**

**As this is a secondary analysis of existing data, no recruitment time is associated with this proposed project.**

## References

1. McPherson, M., P. Arango, H. Fox, C. Lauver, M. McManus, P. Newacheck, J. Perrin, B. Strickland. A new definition of children with special health care needs. *Pediatrics*. 1998;102(1): 117-23.
2. Anderson PJ, Doyle LW. Cognitive and educational deficits in children born extremely preterm. *Semin Perinatology*. 2008;32:51-58.
3. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever B, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birthweight children. *Pediatrics*. 2009;124:717-718.
4. Johnson S, Fawke J, Jennessy E, Rowell V, Thomas S, Wolke D, Marlow N. Neurodevelopmental disability through 11 years of age in children born before 26 weeks gestation. *Pediatrics*. 2009;124:e249-e257.
5. McCormick MC, Litt JS, Smith VC, Zupancic JAF. Prematurity: an overview and public health implications. *Annu Rev Public Health*. 2011;32:15.1-15.13.
6. Saigal S, Stoskopf B, Boyle M, Paneth N, Pinelli J, Streiner D, Goddeeris J. Comparison of current health, functional limitations, and health care use of young adults who were born with extremely low birthweight and normal birthweight. *Pediatrics*. 2007;119:e562-e573.
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**Appendix 1: Question that will serve as data source for dependent variable**

**E. Special Child Services (from NF03)**

**Q1. Is the child receiving or has (s)he received any of the following services:  
(1=No; 2=Received by discontinued; 3=Receiving; 4=Recommended but not receiving)**

- A. Visiting nurse
- B. Home nurse
- C. OT/PT
- D. Speech therapy
- E. Early intervention program
- F. Social worker for child
- G. Specialty medical clinic visits
  - i. Pulmonary
  - ii. Ophthalmological
  - iii. Gastrointestinal
  - iv. Audiologic
  - v. Neurologic
  - vi. ENT
  - vii. Cardiology
  - viii. Urology
  - ix. Neurosurgery
  - x. General Surgery
  - xi. Other
- H. Neurodevelopmental/behavioral clinic visit
- I. NICU Follow Up Clinic (this element will not be incorporated as a dependent variable)

## **Appendix 2: Dependent variable development**

### **Dependent Variables**

- **Dichotomous dependent variable (YES or NO)**
- **Not receiving recommended services (coded “yes” if “4” entered as response by service)**
- **Will develop 1) any unmet need, 2) unmet need by specific group (A-G), and 3) unmet need by each individual service (breaking F. Specialty medical clinic visits into separate components)**
  - A. Visiting nurse or Home nurse**
  - B. OT/PT**
  - C. Speech therapy**
  - D. Early intervention program**
  - E. Social worker for child**
  - F. Specialty medical clinic visits**
    - i. Pulmonary**
    - ii. Opththalmological**
    - iii. Gastrointestinal**
    - iv. Audiologic**
    - v. Neurologic**
    - vi. ENT**
    - vii. Cardiology**
    - viii. Urology**
    - ix. Neurosurgery**
    - x. General Surgery**
    - xi. Other**
  - G. Neurodevelopmental/behavioral clinic visit**

### **Appendix 3: Independent variables**

#### **Independent Variables (will be controlled for in logistic regression models)**

##### **Demographics: (all included in every model)**

- A. Follow-up center**
- B. Year of birth**
- C. Gestational age (by completed week)**
- D. Birthweight (by 100 gram increments)**
- E. Primary language of caregiver**
- F. State supervision of infant/child**
- G. Primary caretaker marital status**
- H. Highest grade completed by primary caretaker**
- I. Employment status of primary and other caretaker**
- J. Has regular source for routine health care (child)**
- K. Child's type of insurance, if any (private, public, both, none)**

##### **Condition characteristics: (based on analyses for collinearity, will develop separate model sets including demographics above and L or M or N below)**

- L. Child has Neurodevelopmental Impairment (NDI) (From NF05 and NF09A – having 1 or more of the following):**
  - a. Neurologic Impairment: Moderate to severe cerebral palsy (CP) with Gross Motor Function Classification System (GMFCS) Level  $\geq 2$**
  - b. Development: Bayley III cognitive score  $< 70$ ; motor score  $< 70$ ; GMFCS Level  $\geq 2$**
  - c. Vision:  $< 20-200$  bilateral**
  - d. Hearing: Permanent hearing loss that does not permit the child to understand the directions of the examiner and communicate +/- amplification with CI or HA**
- M. Child neonatal history (based on Hintz et. al.)**
  - a. Any surfactant therapy**
  - b. Cystic periventricular leukomalacia**
  - c. Intraventricular hemorrhage (by grade)**
  - d. Postnatal corticosteroid usage**
  - e. Necrotizing enterocolitis**
- N. Child current condition (From NF04 – may develop composite variable(s) based on sample size)**
  - a. Use of specific medications over past three months (anti-reflux, asthma/BPD, anticonvulsant/seizure, thyroid, muscle relaxants and/or spasticity – either composite or individual meds based on sample size)**
  - b. Presence of seizures**
  - c. Diagnosed with autism spectrum disorders**

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- d. Use of specific specialized equipment (apnea monitor, oxygen, ventilator/CPAP, gastrostomy tube and/or tube feeding, tracheostomy, pulse oximeter, adapted stroller/wheelchair, braces/orthotics, walker, stander, corner chair or tumble form – either composite or individual based on sample size)**
- e. Presence of oral motor skill difficulty**
- f. Presence of feeding behavior/behavioral difficulties**
- g. Child has hearing impairment**
- h. Child has visual impairment**
- i. Child has cerebral palsy**
- j. Child has congenital or acquired abnormalities**

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**Appendix 4: Potential table shells**

**Table 1. Demographics**

Variable	N (%)
Follow up center	
Year of birth	
Mean Gestational age	
Mean Birthweight	
Child In State supervision	
Primary caretaker marital status	
Married	
Single	
Divorced/widowed	
Educational status of primary caretaker	
Less than 7 <sup>th</sup> grade	
7 <sup>th</sup> to 9 <sup>th</sup> grade	
10 <sup>th</sup> to 12 <sup>th</sup> grade	
High school degree	
Partial college	
College degree	
Employment status of primary caretaker	
Yes, working	
No, not working	
Child has regular source for routine health care	
Child's type of insurance, if any	
Public	
Private	
Both public and private	
Uninsured	
Primary household language	
English	
Spanish	
Other	
Child has Neurodevelopmental Impairment (NDI)	
Child neonatal history	
a. Any surfactant therapy	
b. Cystic periventricular leukomalacia	
c. Intraventricular hemorrhage (by grade)	
d. Postnatal corticosteroid usage	
e. Necrotizing enterocolitis	
Child current condition	
a. Use of specific medications over past three months (anti-reflux, asthma/BPD,	

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Revised: September, 2013

<p><b>anticonvulsant/seizure, thyroid, muscle relaxants and/or spasticity – either composite or individual meds based on sample size)</b></p> <ul style="list-style-type: none"><li><b>b. Presence of seizures</b></li><li><b>c. Diagnosed with autism spectrum disorders</b></li><li><b>d. Use of specific specialized equipment (apnea monitor, oxygen, ventilator/CPAP, gastrostomy tube and/or tube feeding, tracheostomy, pulse oximeter, adapted stroller/wheelchair, braces/orthotics, walker, stander, corner chair or tumble form – either composite or individual based on sample size)</b></li><li><b>e. Presence of oral motor skill difficulty</b></li><li><b>f. Presence of feeding behavior/behavioral difficulties</b></li><li><b>g. Child has hearing impairment</b></li><li><b>h. Child has visual impairment</b></li><li><b>i. Child has cerebral palsy</b></li><li><b>j. Child has congenital or acquired abnormalities</b></li></ul>	
---	--

**Table 2. Service utilization and unmet need**

Service	Received or Receiving N (%)	Recommended but not received N (%)
Visiting nurse or Home nurse		
OT/PT		
Speech therapy		
Early intervention program		
Social worker for child		
<b>Specialty medical clinic visits</b> Pulmonary Ophthalmological Gastrointestinal Audiologic Neurologic ENT Cardiology Urology Neurosurgery General Surgery Other		
Neurodevelopmental/behavioral clinic visit		

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 Revised: September, 2013

**Table 3. Logistic regression models**

**Model Set 1 (Demographics + Neurodevelopmental Impairment)**

Variable	Unmet Need Odds Ratio (SD)						
	Visiting nurse or Home nurse	OT/PT	Speech therapy	Early intervention program	Social worker for child	Specialty medical clinic visits	Neurodevelopmental /behavioral clinic
Follow up center							
Year of birth							
Gestational age							
Birthweight							
Child in State supervision							
Caregiver marital status Married Single Divorced/widowed							
Educational status of primary caretaker Less than 7 <sup>th</sup> grade 7 <sup>th</sup> to 9 <sup>th</sup> grade 10 <sup>th</sup> to 12 <sup>th</sup> grade High school degree Partial college College degree Graduate degree							
Employment status of primary caretaker Yes, working No, not working							
Child has regular source for routine health care							
Child's type of insurance, if any Public							

Private Both public and private Uninsured							
Primary household language English Spanish Other							
Child has Neurodevelopmental Impairment (NDI)							

**Model Set 2 (Demographics + child neonatal history)**

Variable	Unmet Need Odds Ratio (SD)						
	Visiting nurse or Home nurse	OT/PT	Speech therapy	Early intervention program	Social worker for child	Specialty medical clinic visits	Neurodevel- opmental /behavioral clinic
Follow up center							
Year of birth							
Gestational age							
Birthweight							
Child in State supervision							
Caregiver marital status Married Single Divorced/widowed							
Educational status of primary caretaker Less than 7 <sup>th</sup> grade 7 <sup>th</sup> to 9 <sup>th</sup> grade 10 <sup>th</sup> to 12 <sup>th</sup> grade High school degree Partial college College degree							

Graduate degree							
Employment status of primary caretaker Yes, working No, not working							
Child has regular source for routine health care							
Child's type of insurance, if any Public Private Both public and private Uninsured							
Primary household language English Spanish Other							
Any surfactant therapy							
Cystic periventricular leukomalacia							
Intraventricular hemorrhage (by grade)							
Postnatal corticosteroid usage							
Necrotizing enterocolitis							

**Model Set 3 (Demographics + child current condition)**

Variable	Unmet Need Odds Ratio (SD)						
	Visiting nurse or Home nurse	OT/PT	Speech therapy	Early intervention program	Social worker for child	Specialty medical clinic visits	Neurodevelopmental /behavioral clinic
Follow up center							
Year of birth							
Gestational age							

<b>Birthweight</b>							
<b>Child in State supervision</b>							
<b>Caregiver marital status</b> Married Single Divorced/widowed							
<b>Educational status of primary caretaker</b> Less than 7 <sup>th</sup> grade 7 <sup>th</sup> to 9 <sup>th</sup> grade 10 <sup>th</sup> to 12 <sup>th</sup> grade High school degree Partial college College degree Graduate degree							
<b>Employment status of primary caretaker</b> Yes, working No, not working							
<b>Child has regular source for routine health care</b>							
<b>Child's type of insurance, if any</b> Public Private Both public and private Uninsured							
<b>Primary household language</b> English Spanish Other							
<b>Use of specific medications over past three months (either composite or individual meds based on sample size)</b>							
<b>Presence of seizures</b>							
<b>Diagnosed with autism</b>							

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<b>spectrum disorders</b>							
<b>Use of specific specialized equipment (either composite or individual based on sample size)</b>							
<b>Presence of oral motor skill difficulty</b>							
<b>Presence or feeding behavior/behavioral difficulties</b>							
<b>Child has hearing impairment</b>							
<b>Child has visual impairment</b>							
<b>Child has cerebral palsy</b>							
<b>Child has congenital or acquired abnormalities</b>							

**PAS Abstract Evaluation  
Response to Feedback  
September 3, 2013**

**Title:** Unmet Need for Health and Related Services in Extremely Preterm Infants at 18-22 Months of Age

**Authors:** (University of Alabama at Birmingham)  
Preskitt J, Peralta-Carcelen M, Phillips V, Carlo WA

Thank you for the opportunity to revise this protocol. We have included narrative below that addresses the reviewer comments point by point. We have also highlighted the corresponding revisions in the updated proposal narrative.

**Datasets:** GDB  
FU

**Comments from GDB Subcommittee:**  
N/A

**Comments from FU Subcommittee:**

- 1. Sample: The authors state < 27 weeks or < 1000 grams. This will represent a different population for the earlier time periods than the more recent. In the earlier time periods there are larger gestation SGA infants.**

We have revised our inclusion criteria and study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. All infants in the sample will now be subject to the same inclusion criteria – less than 27 weeks gestational age. We will no longer consider birth weight (<1000 grams) as a part of the inclusion criteria. With these modifications, we will no longer have the issue related to larger gestation SGA infants.

- 2. The time period is 1993 to 2011. This gives you a huge sample size. However, it therefore includes different criteria for enrollment in follow-up during the time span and a change in Bayley tests. This needs to be considered since the current children enrolled for Follow-up are < 26 6/7 weeks. In addition, one of your predictors in the regression models is Bayley scores. Besides controlling for center in your regressions, you need to control for year of birth.**

We have revised our study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. This modification will result in the inclusion infants who have similar enrollment criteria (less than 27 weeks

gestation) and all infants in the sample will have been administered the Bayley III. We have added a control variable for year of birth.

**3. Statistical analysis Section. This section needs additional detail with power analysis and rational for using 18 year period.**

We have revised our study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. This revision will eliminate 18 year period. Power analysis has been added on page 4. We have calculated that we need at least 738 infants in the sample for 80% power to find an overall level of unmet need within 5% of the Hintz estimate (alpha at 0.05). With our study window, we estimated having 800-900 infants in the sample. A preliminary query (database query 8/29/13) shows 1488 infants have completed Follow Up Study Status Forms (NF10). This includes infants who were lost to follow up and those who died post discharge. Assuming an 84% follow up rate, this would yield a sample size of about 1250 infants. We have therefore exceeded the estimated sample size and statistical power is above 95% to estimate unmet need within +/- 5% of the Hintz estimate (36.5%).

**4. The protocol has tremendous overlap with the 2008 NRN paper of Hintz et al. "Community Supports after Surviving Extremely Low-Birth-Weight, Extremely Preterm Birth", in which the outcomes, tables and regressions are similar.**

We have revised our study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. This revision will eliminate sample overlap with Hintz. Further, while Hintz looked at perceived need based on a question for each service that asked the caregiver whether the child "needs" the service, we have limited our inclusion criteria such that only children who received the revised version of this question will be in the sample. The revision, as clarified in the study protocol manual, specifies that the question relates to services that were recommended by a medical professional. Therefore, we will be looking at factors associated with not receiving services that were recommended by a medical professional. We have revised and clarified our proposal to exclusively focus on unmet needs for health and related services overall and by specific service type, as well as identification of factors associated with unmet need.

**5. The time period of the Hintz study was 1997 to 2000. There is a 4 year overlap in subjects.**

We have revised our inclusion criteria and study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. This revision will eliminate overlap with Hintz in terms of the sample window and subjects.

**6. The Hintz study showed an overall incidence of 36% for unmet needs, the most common was speech and language services at 24%. This value is more relevant than**

**the 19.8% reported by National Survey of Children with Special Health Care Needs, which is quoted by the authors.**

The original omission of the Hintz article was inadvertent. In light of those findings and this reviewer comment, we have revised our hypothesis related to overall level of unmet need (one or more services recommended by a medical professional but not received) to reflect the baseline figures from Hintz and colleagues (36.5%). See page 1 of the proposal. We have included rates from the Hintz article in addition to those from the National Survey of Children with Special Health Care Needs. We have also revised our hypothesis related to overall rates of unmet needs to the 36.5% baseline value found by Hintz and colleagues.

**7. Needs to be more focused to avoid overlap with Hintz study and avoid heterogeneous Bayley and NDI outcomes. Could submit for reconsideration, with no guarantee.**

We have revised our inclusion criteria and study window to infants born at less than 27 weeks gestation who completed their 18-22 months follow up visit between 4/1/2011 to 7/31/2013. This revision will eliminate the overlap with Hintz study sample and will avoid issues pertaining to heterogeneity in enrollment criteria, Bayley version, and NDI outcomes. This more focused timeframe and inclusion criteria will result in:

- all infants in the sample are subject to the same inclusion criteria,
- all infants in the sample will have Bayley III scores, if successfully tested, and
- all infants in the sample subject to present definition for NDI outcome, as outlined in the Follow-Up Study manual (also presented in Appendix 3, item L).

Further, the project has been more precisely focused to avoid conceptual and outcome overlap with previous literature. Please refer to the overall proposal narrative. Specific contributions include:

- More recent data,
- Focus on unmet need for services recommended by a medical professional,
- Focus on unmet need overall and for specific services, and
- Focus on factors associated with unmet need overall and for specific services – includes demographics, neonatal history, neurodevelopmental impairment, and current conditions.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Friday, September 06, 2013 12:53:32 PM

---

24 consent forms.

What is DBSD?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, September 06, 2013 12:53 PM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI

So only 24 consent forms?

But the (b)(5)

---

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, September 06, 2013 12:51 PM  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI

RTI does not submit a consent form – I just clarified this.

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 12:47 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

That would be a (b)(5)

(b)(5)

You probably should check with RTI on this one:

"Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25?"

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 12:44 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

I believe it is (b)(5)

(b)(5)

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 12:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

So, the IRB for the DCC didn't approve consent forms, correct? Did they just approve participation in the study?

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 12:41 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

24 consent forms from 24 hospital or center IRB's. One IRB approval for the DCC making it 25 IRB approvals.

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, September 06, 2013 12:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Hi Rose. Please see below.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Friday, September 06, 2013 12:37 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: CBS News questions regarding RTI

More!

Sent from my BlackBerry 10 smartphone.

---

**From:** [mylesr@od.nih.gov](mailto:mylesr@od.nih.gov)  
**Sent:** Friday, September 6, 2013 12:35 PM  
**To:** Skeen, Kim  
**Subject:** Re: CBS News questions regarding RTI

I believe that the 25 IRBs were specifically involved with the SUPPORT study but I'll definitely confirm for you.

Sent from my BlackBerry 10 smartphone.

---

**From:** Skeen, Kim  
**Sent:** Friday, September 6, 2013 12:27 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Renate,

The story will NOT air this Sunday but beyond that we don't yet know yet. We want to clarify that 25 IRB's approved consent forms are for SUPPORT specifically (not just that there are 25 IRB's in the network). Also RTI said they did NOT approve a consent form and have no IRB. Is RTI the Data Coordinating Center you are counting in the 25? Please clarify. Thanks.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Myles, Renate (NIH/OD) [E] [<mailto:mylesr@od.nih.gov>]  
**Sent:** Friday, September 06, 2013 11:17 AM  
**To:** Skeen, Kim  
**Subject:** RE: CBS News questions regarding RTI

Hi Kim:

My pleasure! There are 25 IRBs in total including 1 at the Data Coordinating Center. All of the sites listed in the NEJM article have one except for the Utah site, which has 2, and the University of Cincinnati site, which has 3.

I'll have to check with our experts on your last two questions. I'll get back to you ASAP.

Are you expecting the piece to air this Sunday morning?

Thanks,  
Renate

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Friday, September 06, 2013 10:57 AM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Renate,

Thank you so much for all the information.

- For your background: on the IRB question, we just want to have the right number as to how many IRB's approved SUPPORT consent forms (and we want to have contacted all of them.) Some accounts say 21, 22 or 23 but they might be counting NIH which isn't an IRB and RTI which isn't an IRB. What is the correct number of IRB's for the SUPPORT study?

- We have a list of 21 (counting University of Texas Southwestern Medical Center Dallas and University of Texas Health Science Center Houston as one).
  - Is RTI the Data Coordinating Center? (We didn't count RTI as an IRB because they said they don't have an IRB.)
- With whom has the SUPPORT data been shared? For your background, we want to know what corporate entities had interest in the study whether directly or indirectly.
  - Lastly, was the same surfactant used in all the babies who were randomized to receive surfactant? If so, which surfactant? If not, please detail.

Much appreciated,

Kim  
Producer  
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(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

- 1. How many institutional review boards (IRB's) approved the SUPPORT study? Many press reports cite 23 as the number of institutions participating in the study. But we want to know how many IRB's there were (excluding RTI because they say they did not review consent forms and not counting NIH since they were not an IRB.) Here is a list of SUPPORT study IRB's we have compiled—please confirm that it is complete and accurate.**

The Neonatal Network has a total of 25 IRBs; this includes 1 for the Data Coordinating Center. Note that some institutions in the network have more than one IRB.

- 2. What is the official title of the SUPPORT study and what universities are participating in SUPPORT?**

Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT). This NEJM article lists the SUPPORT Study participants at the time:

<http://www.nejm.org/doi/full/10.1056/NEJMoa0911781#t=article>

- 3. How much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects?**

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

Best,  
Renate

**Renate Myles, MBA**  
Acting Chief  
News Media Branch  
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**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:bistreich@rti.org>]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,

Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,

RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
**Sent:** Wednesday, September 04, 2013 11:24 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,

I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this

study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:50 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: Is this page up to date?

Not that I know of. But, then again, she's a reporter, so she can handle the problem of what's succinct or not.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 4:49 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Is this page up to date?

Good point. She definitely wants the participants for OHRP issue. The only problem is that NEJM paper doesn't list them succinctly. Are they listed anywhere else? If not, I'll point to the NEJM article.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:47 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: Is this page up to date?

I don't know what she wants the list for. So you should (b)(5)

(b)(5)

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 4:38 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Is this page up to date?

Should I just include the (b)(5)

(b)(5)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:34 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: Is this page up to date?

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:34 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Is this page up to date?

The link you provided has the current sites as well as collaborating sites.

The attached paper from NEJM has the sites that participated in SUPPORT (page 9-10 in the paper)

Rosemary D. Higgins, MD

**Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch**

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6100 Executive Blvd., Room 4B03

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301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Bock, Robert (NIH/NICHD) [E]

**Sent:** Thursday, September 05, 2013 4:31 PM

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

**Subject:** Is this page up to date?

The CBS reporter had wanted us to confirm the participating sites.

Is the listing at the bottom of this page up to date? (I'd prefer to send her links to published materials, if I can.)

<http://www.nichd.nih.gov/research/supported/Pages/nrn.aspx>

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:34 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: Is this page up to date?  
**Attachments:** Carlo, SUPPORT, 2010-05-16.pdf

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:34 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Is this page up to date?

The link you provided has the current sites as well as collaborating sites.

The attached paper from NEJM has the sites that participated in SUPPORT (page 9-10 in the paper)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:31 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Is this page up to date?

The CBS reporter had wanted us to confirm the participating sites.

Is the listing at the bottom of this page up to date? (I'd prefer to send her links to published materials, if I can.)

<http://www.nichd.nih.gov/research/supported/Pages/nrn.aspx>

ORIGINAL ARTICLE

## Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD  
Neonatal Research Network\*

### ABSTRACT

#### BACKGROUND

Previous studies have suggested that the incidence of retinopathy is lower in preterm infants with exposure to reduced levels of oxygenation than in those exposed to higher levels of oxygenation. However, it is unclear what range of oxygen saturation is appropriate to minimize retinopathy without increasing adverse outcomes.

#### METHODS

We performed a randomized trial with a 2-by-2 factorial design to compare target ranges of oxygen saturation of 85 to 89% or 91 to 95% among 1316 infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. The primary outcome was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before discharge from the hospital, or both. All infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant.

#### RESULTS

The rates of severe retinopathy or death did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3% and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06;  $P=0.21$ ). Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9% of infants vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60;  $P=0.04$ ), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73;  $P<0.001$ ). There were no significant differences in the rates of other adverse events.

#### CONCLUSIONS

A lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern, since a lower target range of oxygen saturation is increasingly being advocated to prevent retinopathy of prematurity. (ClinicalTrials.gov number, NCT00233324.)

\*The authors are listed in the Appendix. The affiliations of the authors and other investigators in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development are listed in the Appendix. Address reprint requests to Dr. Waldemar A. Carlo at the University of Alabama at Birmingham, 176F Suite 9380, 619 S. 19th St., Birmingham, AL 35294-7335, or at wcarlo@peds.uab.edu.

This article (10.1056/NEJMoa0911781) was published on May 16, 2010, at NEJM.org.

N Engl J Med 2010.

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**R**ETINOPATHY OF PREMATURETY IS AN important cause of blindness and other visual disabilities in preterm infants. The incidence of retinopathy of prematurity was increased with exposure to unrestricted oxygen supplementation in preterm infants in randomized, controlled trials performed in the 1950s.<sup>1</sup> In the 1960s, this increase resulted in the practice of restricting the fraction of inspired oxygen (FIO<sub>2</sub>) to no more than 0.50, which was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup> More recent data suggest that levels of oxygen saturation previously thought to be at the upper end of the normal range may increase the risk of retinopathy of prematurity as compared with levels at the lower end of the normal range.<sup>3-5</sup> Oxygen toxicity may also increase the risk of death,<sup>6,7</sup> bronchopulmonary dysplasia,<sup>8-10</sup> periventricular leukomalacia,<sup>11</sup> cerebral palsy,<sup>12</sup> and other conditions. Although a multicenter observational study did not show a significant association between higher values for the partial pressure of arterial oxygen and retinopathy, a single-center cohort study involving transcutaneous oxygen monitoring provided support for an association between an increased risk of retinopathy<sup>13</sup> and exposure to arterial oxygen levels of 80 mm Hg or more.<sup>14</sup>

Pulse oximetry allows clinicians to continuously monitor levels of oxygen saturation and to target levels in a defined range. Associations between lower target levels of oxygen saturation and a lower incidence of retinopathy have been reported.<sup>1-5</sup> In a survey of 144 neonatal intensive care units (NICUs), the rate of retinal ablation surgery among very-low-birth-weight infants was increased among infants cared for in NICUs that used higher maximum target levels of oxygen saturation, as compared with infants in NICUs that used lower target levels. The rate of retinal ablation surgery was 3.3% in NICUs using target levels of 92% or higher and 1.4% in NICUs using target levels of less than 92%; the rate was 5.6% in NICUs using target levels of 98% or higher and 3.1% in NICUs using target levels of less than 98%.<sup>3</sup> In a retrospective study comparing outcomes at five NICUs, the incidence of severe retinopathy requiring ablation therapy was 27% in NICUs where the target saturation level was 88 to 98% and only 6% in NICUs where the target level was 70 to 90%.<sup>3</sup> Rates of death and cerebral

palsy did not differ significantly among these NICUs. In three studies with a before-and-after design, the implementation of a policy of target levels of oxygen saturation of approximately 83 to 95% was associated with a substantial reduction in the incidence of retinopathy, as compared with the period before implementation of the policy; however, the actual levels of oxygen saturation achieved, mortality, and neurodevelopmental outcomes were not reported.<sup>4,15,16</sup> Although data from these studies suggest that maintenance of oxygenation at ranges lower than those previously used may decrease the incidence of retinopathy of prematurity, the safety of low target levels of oxygen saturation remains a concern.

We conducted the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a controlled, multicenter trial with a 2-by-2 factorial design, to compare two target levels of oxygen saturation and two ventilation approaches (continuous positive airway pressure [CPAP] initiated in the delivery room with a protocol-driven strategy of limited ventilation vs. intratracheal administration of surfactant with a protocol-driven strategy of conventional ventilation). The oxygen-saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation. The ventilation part of this factorial-design trial, which was used to control the ventilation approach and test other hypotheses, is reported elsewhere in this issue of the *Journal*.<sup>17</sup>

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## METHODS

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### STUDY DESIGN

The study was conducted as part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The study was approved by the institutional review board at each participating site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Data collected at the study sites were transmitted to RTI International, which stored, managed, and analyzed the data for this

OXYGEN SATURATION AND OUTCOMES OF PREMATURETY

study. Written informed consent was obtained from the parent or guardian of each child before delivery.

**PATIENTS**

Infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation were eligible for enrollment at birth. Infants born in other hospitals and those known to have major congenital anomalies were excluded.

**ENROLLMENT AND TREATMENT**

Infants were enrolled from February 2005 through February 2009. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Using sealed, opaque envelopes, we randomly assigned infants before birth to a target range of oxygen saturation of 85 to 89% (the lower-oxygen-saturation group) or 91 to 95% (the higher-oxygen-saturation group). Infants who were part of multiple births were randomly assigned to the same group.

Blinding was maintained with the use of electronically altered pulse oximeters (Masimo Radical Pulse Oximeter) that showed saturation levels of 88 to 92% for both targets of oxygen saturation, with a maximum variation of 3%. For example, a reading of 90% corresponded to actual levels of oxygen saturation of 87% in the group assigned to lower oxygen saturation (85 to 89%) and 93% in the group assigned to higher oxygen saturation (91 to 95%). A previous trial used a fixed 3% absolute oxygen-saturation variation throughout the entire range of saturation levels to keep caregivers unaware of study-group assignments and to separate levels of oxygen saturation in preterm infants,<sup>18</sup> but the algorithm used in the current trial differed, since the oxygen-saturation reading gradually changed and reverted to actual (non-skewed) values when it was less than 84% or higher than 96% in both treatment groups. Limits of 85% and 95% that would trigger an alarm in the delivery system were suggested, but they could be changed for individual patients.

Targeting of levels of oxygen saturation with altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the in-

fant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age. Adjustments in supplemental oxygen to maintain the target level of oxygen saturation between 88 and 92% were performed by the clinical staff rather than the research staff.

Data on oxygen saturation were electronically sampled every 10 seconds and downloaded by the data center. Readings of levels of oxygen saturation that were pooled (i.e., not separated according to treatment group) were provided quarterly to each center for feedback on compliance. Actual data on oxygen saturation were not provided to the clinicians or researchers but are used exclusively in this article. For the ventilation part of this trial with a 2-by-2 factorial design, participants were randomly assigned to CPAP with a protocol-driven limited ventilation strategy or to prophylactic early administration of surfactant with a protocol-driven conventional ventilation strategy.<sup>17</sup>

**ASSESSMENTS**

Research nurses recorded all data using standardized definitions included in the trial's manual of operations. Data collection, excluding examinations to detect retinopathy of prematurity, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group<sup>19,20</sup>) was diagnosed if any of the following findings were present: in zone 1, stage 3 retinopathy of prematurity, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of retinopathy of prematurity; in zone 2, plus disease with stage 2 retinopathy of prematurity or plus disease with stage 3 retinopathy of

prematurity. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. The primary outcome was death before discharge or severe retinopathy as defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. The original study protocol specified a primary outcome of death before 36 weeks of postmenstrual age, but this was changed to death before discharge before any data analyses were performed. All other outcomes reported were prespecified, including assessment of the need for oxygen at 36 weeks of postmenstrual age<sup>21</sup> and safety outcomes.

#### STATISTICAL ANALYSIS

The analysis for the oxygen-saturation part of this factorial trial compared the percentage of infants in each treatment group in whom the primary outcome of severe retinopathy or death occurred. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. We performed a post hoc survival analysis with the use of a Cox proportional-hazards model to compare mortality in the two oxygen-saturation groups, assuming that there were no subsequent deaths among the infants who were discharged. In the analysis of all outcomes, the results were adjusted, as prespecified, for stratification according to study center and gestational age, as well as for familial clustering due to random assignment of infants who were part of multiple births to the same treatment group. To compare the actual oxygen-saturation values in the two treatment groups, the median value during oxygen supplementation was determined for each infant. Those values were plotted according to treatment group, and the medians of the resulting distributions were compared with the use of a rank-sum test.

An absolute between-group difference of 10 percentage points in the rate of the composite primary outcome was considered clinically important. The sample-size calculations were based on the rate of death or threshold retinopathy of 47% in the Neonatal Research Network for the year

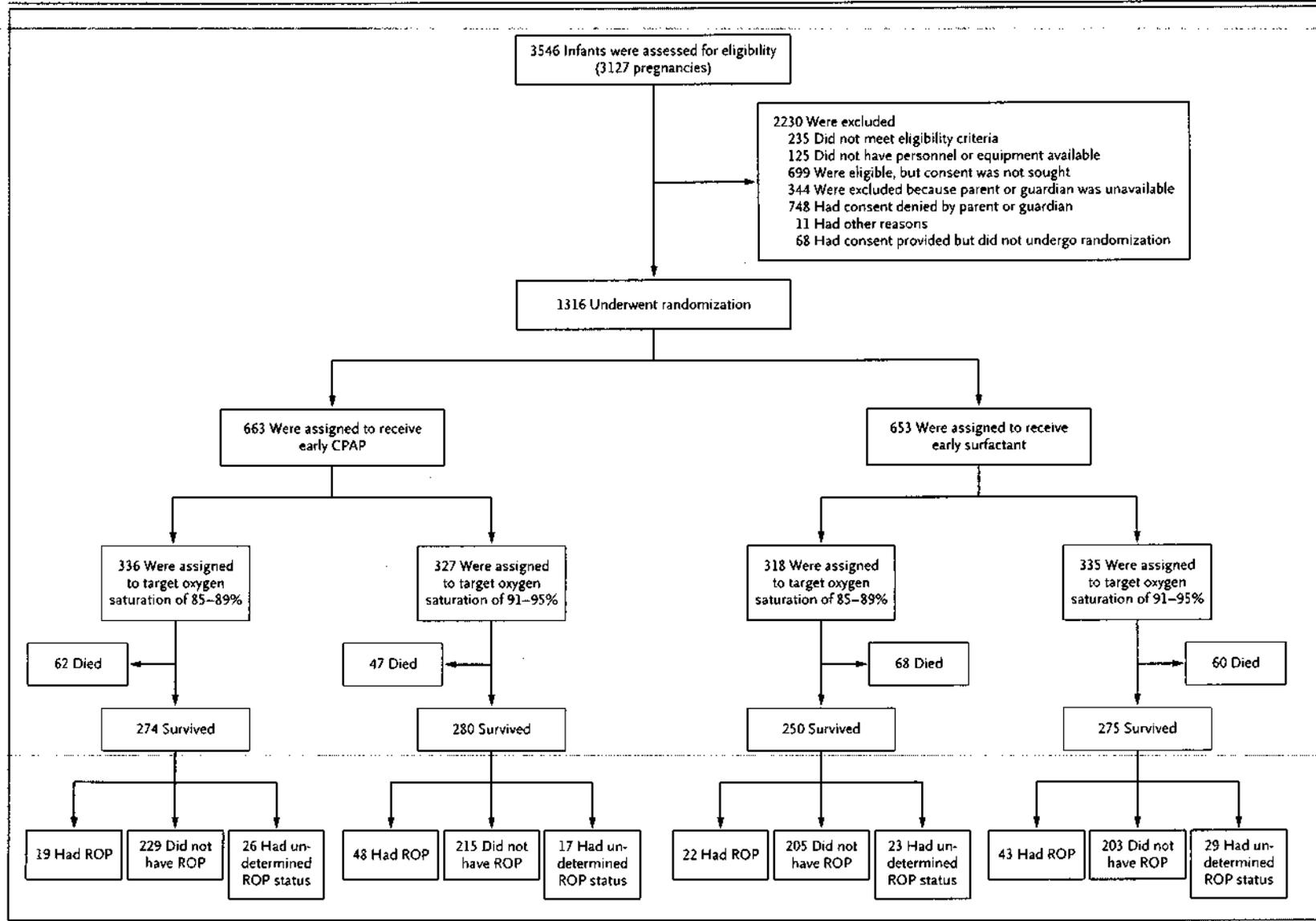
#### Figure 1 (facing page). Screening, Randomization, and Primary Outcome.

The numbers shown exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. The outcome of severe retinopathy of prematurity (ROP) could not be determined in some infants because of loss to follow-up. CPAP denotes continuous positive airway pressure.

2000. We increased the sample size by a factor of 1.12 to allow for infants who were part of multiple births to be randomly assigned to the same treatment (since this introduced a clustering effect into the design), and we increased the sample size by an additional 17% to adjust for attrition after hospital discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. The study was not powered to detect an interaction effect between the two factorial parts of the study.

Analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned analyses of secondary outcomes according to treatment group, we would expect no more than three tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for predefined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have P values of less than 0.05 on the basis of chance alone.

An independent data and safety monitoring committee appointed by the director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the data and safety monitoring committee, at the request of the investigators, evaluated the data on oxygen saturation to evaluate compliance with the protocol. The Lan-DeMets spend-



10.1056/NEJM09091781 NEJM.ORG

Table 1. Baseline Characteristics of the Patients.		
Characteristic	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)
Birth weight — g	836±193	825±193
Gestational age — wk	26±1	26±1
Male sex — no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group — no./total no. (%)†		
Non-Hispanic white	242/654 (37.0)	279/662 (42.1)
Non-Hispanic black	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	633/654 (96.8)	632/661 (95.6)
Full course	477/651 (73.3)	462/658 (70.2)
Apgar score <3 at 5 min — no./total no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant treatment — no./total no. (%)	531/653 (81.3)	558/660 (84.5)
Multiple birth — no./total no. (%)	161/654 (24.6)	176/662 (26.6)

\* Plus-minus values are means ±SD. P>0.05 for all comparisons.

† Race or ethnic group was reported by the mother or guardian of each child.

ing functions with Pocock and O'Brien-Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. In the final analysis, the nominal level of significance was 0.05. The monitored safety outcomes included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

## RESULTS

### CHARACTERISTICS OF THE STUDY SAMPLE

We enrolled 1316 infants in the study (Fig. 1). When 247 infants had been enrolled, enrollment was temporarily suspended on the basis of the recommendation of the data and safety monitoring committee and the decision of the director of the National Institute of Child Health and Human Development because of concern that readings of levels of oxygen saturation often exceeded the target levels. Separation of the oximetry data according to whether patients were breathing ambient air or receiving oxygen supplementation addressed this concern, because infants who did not require supplemental oxygen accounted for a large proportion of the high saturation levels. Resump-

tion of enrollment was approved. The baseline characteristics of the two treatment groups were similar (Table 1).

### PRIMARY OUTCOME

The rate of the composite primary outcome, severe retinopathy or death before discharge, did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3 and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21) (Table 2). Although the trial was not powered to detect an interaction between the level of oxygen saturation and the ventilation intervention, we prospectively planned to evaluate this interaction, and no significant interaction was found (P=0.57). Death before discharge occurred in 130 of 654 infants in the lower-oxygen-saturation group (19.9%) as compared with 107 of 662 infants in the higher-oxygen-saturation group (16.2%) (relative risk with lower oxygen saturation, 1.27; 95% CI, 1.01 to 1.60; P=0.04; number needed to harm, 27). The distribution of the major causes of death did not differ significantly between the two groups (see Table 1 in the Supplementary Appendix, available with the

OXYGEN SATURATION AND OUTCOMES OF PREMATUREITY

Table 2. Major Outcomes.*			
Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	<i>no./total no. (%)</i>		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76–1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37–0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01–1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99–1.63)
BPD, defined by use of supplemental oxygen, at 36 wk	203/540 (37.6)	265/568 (46.7)	0.82 (0.72–0.93)
BPD, defined by use of supplemental oxygen, or death by 36 wk	317/654 (48.5)	359/662 (54.2)	0.91 (0.83–1.01)
BPD, physiological definition, at 36 wk †	205/540 (38.0)	237/568 (41.7)	0.92 (0.81–1.05)
BPD, physiological definition, or death by 36 wk †	319/654 (48.8)	331/662 (50.0)	0.99 (0.90–1.10)
Intraventricular hemorrhage, grade 3 or 4 ‡	83/630 (13.2)	81/640 (12.7)	1.06 (0.80–1.40)
Intraventricular hemorrhage, grade 3 or 4, or death ‡	179/653 (27.4)	156/661 (23.6)	1.18 (0.99–1.42)
Periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49–1.42)
Periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96–1.45)
Necrotizing enterocolitis, stage ≥2 §	76/641 (11.9)	70/649 (10.8)	1.11 (0.82–1.51)
Necrotizing enterocolitis, stage ≥2, or death §	176/654 (26.9)	155/662 (23.4)	1.18 (0.98–1.43)
Pneumothorax	47/654 (7.2)	43/662 (6.5)	1.12 (0.74–1.68)
Postnatal corticosteroids for BPD	61/636 (9.6)	69/644 (10.7)	0.91 (0.67–1.24)
Death			
By 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72–1.72)
By 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84–1.70)
Late-onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89–1.18)
Late-onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94–1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86–1.07)
Treatment for patent ductus arteriosus			
Medical	219/634 (34.5)	233/645 (36.1)	0.95 (0.82–1.09)
Surgical	73/641 (11.4)	68/648 (10.5)	1.09 (0.80–1.48)
Any air leaks in first 14 days	51/654 (7.8)	42/662 (6.3)	1.23 (0.83–1.83)

\* Values were adjusted for stratification factors (study center and gestational-age group) as well as for familial clustering. BPD denotes bronchopulmonary dysplasia.

† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% oxygen or the need for positive pressure support at 36 weeks or, in the case of infants requiring less than 30% oxygen, the need for any oxygen at 36 weeks after an attempt at oxygen withdrawal.

‡ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.

§ There are three stages of necrotizing enterocolitis; higher stages indicate more severe necrotizing enterocolitis.

full text of this article at NEJM.org). Similar results were observed for both gestational-age strata. Survival analysis with the use of the unadjusted Kaplan–Meier method (Fig. 2) and a Cox proportional-hazards model produced similar results (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07).

The rate of severe retinopathy among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower-oxygen-saturation group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001; number needed to treat, 11). Although

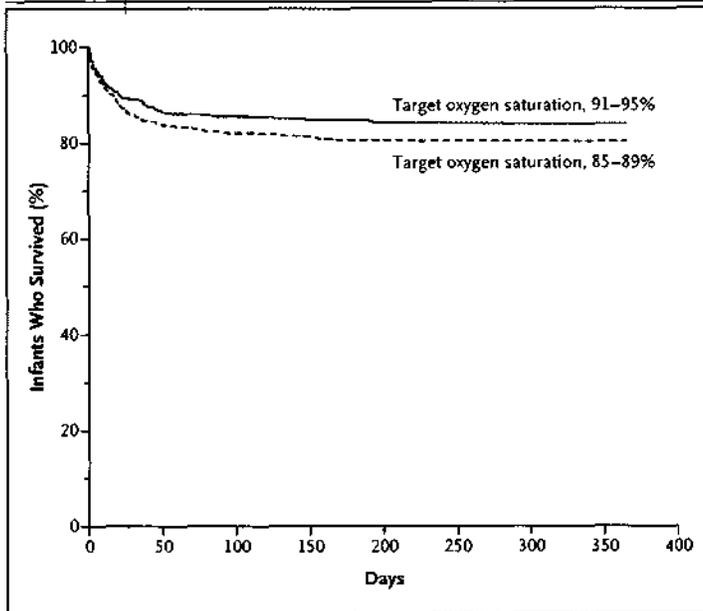


Figure 2. Kaplan-Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

Cox proportional-hazards analysis indicated that there was an increased hazard of death in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (hazard ratio, 1.28; 95% CI, 0.98 to 1.68;  $P=0.07$ ). The analysis assumed that infants who were discharged or transferred from the hospital survived to 1 year of age.

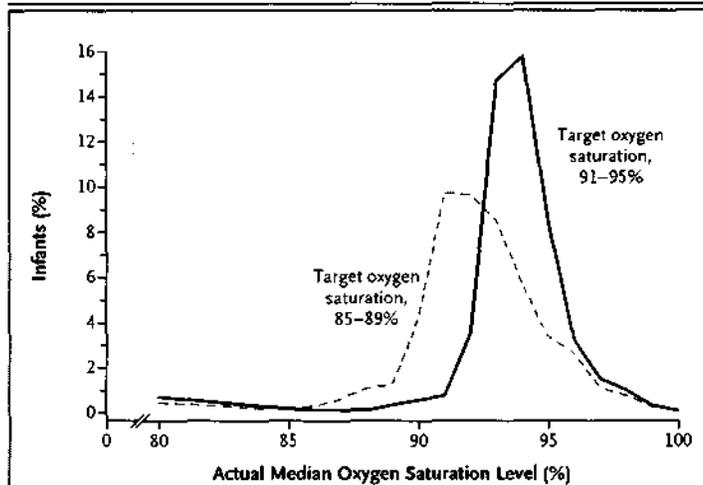


Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.

The medians of the distributions were significantly different on the basis of a rank-sum test ( $P<0.001$ ). The 80% level of oxygen saturation shown includes all values at or below 80%.

opathy or surgical intervention for retinopathy. Three ophthalmologists adjudicated results for the patients who did not meet the criteria for retinopathy, and the results were materially unchanged (Table 2 in the Supplementary Appendix).

#### SECONDARY OUTCOMES

The rate of oxygen use at 36 weeks was reduced in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group ( $P=0.002$ ), but the rates of bronchopulmonary dysplasia among survivors, as determined by the physiological test of oxygen saturation at 36 weeks, and the composite outcome of bronchopulmonary dysplasia or death by 36 weeks did not differ significantly between the treatment groups. Other prespecified major outcomes also did not differ significantly between the two groups (Table 2).

The median level of oxygen saturation in infants who were receiving oxygen supplementation in the two treatment groups differed substantially but, as expected, there was considerable overlap (Fig. 3). The actual median levels of oxygen saturation were slightly higher than targeted levels in both treatment groups. The duration of oxygen supplementation was shorter in the lower-oxygen-saturation group, but the duration of mechanical ventilation, CPAP, and nasal synchronized intermittent mandatory ventilation did not differ significantly (Table 3 in the Supplementary Appendix). Other measures of resource use also did not differ significantly between the two groups.

#### DISCUSSION

In this multicenter, randomized trial, we found no significant difference in the primary outcome — severe retinopathy or death — between infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) and those assigned to a higher target range (91 to 95%). Assessment of the individual components of the primary outcome showed that the lower target range of oxygen saturation increased the risk of in-hospital death, whereas it reduced the risk of severe retinopathy among survivors. These results were observed even though there was substantial overlap of actual levels of oxygen saturation between the two treatment groups. Previous trials of targeting of levels of oxygen saturation have shown similar difficulties in maintaining levels of oxygen saturation within a narrow target range.<sup>18,22</sup> Longer follow-up will be required to determine

use of bevacizumab was among the criteria for this outcome, only three infants received bevacizumab, and these infants also had threshold retin-

OXYGEN SATURATION AND OUTCOMES OF PREMATUREITY

the effects of lower target ranges of oxygen saturation on functional visual and neurodevelopmental outcomes.

Despite the increase in mortality when restrictive oxygen supplementation was used in the 1950s and 1960s and the limited data from observational studies,<sup>3-5,15,16</sup> it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of retinopathy of prematurity.<sup>23</sup> The results of this large randomized trial to test the effect of lower versus higher target ranges of oxygen saturation, in conjunction with the results of previous studies, add to the concern that oxygen restriction may increase the rate of death among preterm infants. The combined risk difference observed in the trials from the 1950s was an absolute increase in in-hospital mortality of 4.9 percentage points in the oxygen-restricted group,<sup>1</sup> which is close to the absolute increase of 3.7 percentage points in the rate of death before discharge in the lower-oxygen-saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants at least 2 weeks after birth<sup>18</sup> or after moderately severe retinopathy developed<sup>22</sup> did not show an increased risk of death or a significantly reduced risk of retinopathy in the lower-oxygen-saturation groups. However, the lower target ranges of oxygen saturation in these trials — 91 to 94% in one trial and 89 to 94% in the other — were closer to the target range in our higher-oxygen-saturation group. The increase in mortality in our trial may be related to the lower target ranges of levels of oxygen saturation, the use of oxygen restriction started soon after birth, or both. A meta-analysis of early restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a reduction in severe retinopathy (relative risk, 0.19; 95% CI, 0.07 to 0.50) with a nonsignificant trend toward increased mortality.<sup>24</sup> These trials were performed by limiting the  $\text{FiO}_2$  concentration usually to less than

0.50, at a time before the continuous monitoring of arterial oxygen saturation was possible. To our knowledge, no other randomized, controlled trials of different target ranges of oxygen saturation in supplementation initiated soon after birth have been performed since the availability of continuous transcutaneous monitoring of oxygen saturation. Like the meta-analysis<sup>24</sup> and most non-randomized studies,<sup>3-5,15,16</sup> our trial confirmed that lower target ranges of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented. Several ongoing trials across the world address the same intervention tested in the current trial.<sup>25</sup>

In summary, a target range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, did not affect the combined outcome of severe retinopathy or death, but it increased mortality while substantially decreasing severe retinopathy among survivors. At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.

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Dr. Van Meurs reports receiving reimbursement for travel expenses from Ikarria Holdings. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 4:27 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: RE: CBS News questions regarding RTI

I can never remember. (What would we do without Google?)

**Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)**

<http://clinicaltrials.gov/show/NCT00233324>

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 4:26 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: RE: CBS News questions regarding RTI

And what's the official name of the SUPPORT study?

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 3:53 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

The response to Kim's note at bottom.

Total NICHD funding for FY 2012 for the Neonatal Research Network was \$11,886,753. This covers the 10 studies currently under way in the network. Of the \$11,886,753 total, the network sites received \$5,577,976. The Data Coordinating Center received \$6,308,777. Of this \$6,308,777 figure, approximately \$3 million was for operating expenses and the Data Coordinating Center allocated the remainder to the network sites, on a per patient basis, to cover part of the cost of patient recruitment and enrollment. The remainder of patient recruitment and enrollment costs was derived from the centers' budget of \$5,577,976.

The data is owned by the NICHD Neonatal Research Network Steering Committee and the Network determines its use. The data is not sold, but can be made available for research protocols approved by the Network.

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

**John and Diane,**

**Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?**

**Thank you.**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]  
**Subject:** RE: Trying again: CBS News Question Regarding RTI  
**Date:** Thursday, September 05, 2013 3:43:00 PM

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sure

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**Sent:** Thursday, September 05, 2013 3:42 PM  
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**Subject:** RE: Trying again: CBS News Question Regarding RTI

Can we just (b)(5)

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 3:41 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]  
**Subject:** RE: Trying again: CBS News Question Regarding RTI

We need to state that (b)(5)

Otherwise looks ok

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]

**Sent:** Thursday, September 05, 2013 3:37 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]  
**Subject:** Trying again: CBS News Question Regarding RTI

The response to Kim's note below, before I send it on to Renate:

(b)(5)

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

Please see the emails below and provide answers to these questions: how much funding does NIH provide to RTI, with whom and how was data shared or sold regarding the SUPPORT study and, more generally, with whom and how is RTI data shared regarding other projects? Can you please let us know today?

Thank you.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Thursday, September 05, 2013 3:08:15 PM  
**Attachments:** image001.png

---

- The data is that of the NICHD Neonatal Research Network Steering Committee and the Network determines its use.

Since RTI does not recruit patients, they do not have an approved consent form

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 2:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Please see attached. I think we need to clarify her second bullet point.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 2:28 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi Bob:

Sorry, I've been tied up in meetings. RTI responded with a rather curt answer which I wanted to share with you. Can you take a look and see if the information below still applies?

Renate

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 2:12 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: CBS News questions regarding RTI

OK. Someone will need to (b)(5)

(b)(5)

Please let us see any changes you make to the above before you send it, so that we can vet it with Dr. Higgins.

Thanks.

Bob

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 12:50 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

And another question about RTI.

---

**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 12:48 PM  
**To:** 'Skeen, Kim'; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi, Kim—We'll be back to you later.

Thanks,

John

**John Burklow**  
Associate Director for Communications and Public Liaison  
National Institutes of Health  
Building 1, Room 344  
(301) 496-4461 (phone)  
(301) 496-0017 (fax)  
[burklowj@od.nih.gov](mailto:burklowj@od.nih.gov)



**Celebration of Science at NIH:** *watch how medical research saves lives and improves health*

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
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Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH—and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**From:** Bistreich-Wolfe, Lisa [mailto:lbistreich@rti.org]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

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**From:** Skeen, Kim [mailto:SkeenK@cbsnews.com]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [mailto:[l.bistreich@rti.org](mailto:l.bistreich@rti.org)]  
**Sent:** Wednesday, September 04, 2013 11:24 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
I got your voicemail and email. RTI's role in the SUPPORT study is described here.

[RTI International's Role in the NICHD Neonatal Network SUPPORT Study](#)

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim [SMTP: SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Luc Brion  
**To:** Wally Carlo, M.D.; Barbara Stoll  
**Cc:** [REDACTED]@gmail.com>; Wraga, Lisa Ann; Wraga, Lisa Ann; <nfiner@ucsd.edu>; Roy Heyne; Roy Heyne; Gantz, Marie; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Das, Abhik; Gantz, Marie; Gantz, Marie; Mambarambath Jaleel; Mambarambath Jaleel; Myra Wyckoff; Myra Wyckoff  
**Subject:** RE: FW: PEDIATRICS: Decision Letter for MS ID 2013-2023  
**Date:** Thursday, September 05, 2013 2:44:38 PM

---

This is what we had decided from the beginning, because of large inter-institutional differences observed in most NRN studies. To compare before versus after we had to use only the 11 centers.

How about the following:

In contrast with participation in other neonatal networks such as the Vermont Oxford Network, the Pediatrix Network and the California Perinatal Quality Care Collaborative, NRN participation requires eligible centers to submit an application to the NICHD every 5 years; at each cycle some centers leave the NRN and other centers are being recruited. Limitation of the data to centers that stayed in the NRN during the two periods of the study allowed us to analyze center-specific changes after SUPPORT as well as changes in the entire sample. However, results from this study may not reflect those that could have been obtained had we assessed the entire NRN population because all the exclusions resulted in analyzing only a limited proportion of patients born in the NRN.

Luc

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, September 05, 2013 1:09 PM  
**To:** Barbara Stoll; Luc Brion; Luc Brion  
**Cc:** [REDACTED]@gmail.com>; ; Wraga, Lisa Ann; Wraga, Lisa Ann; <nfiner@ucsd.edu>; ; Roy Heyne; Roy Heyne; Gantz, Marie; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Das, Abhik; Gantz, Marie; Gantz, Marie; Mambarambath Jaleel; Mambarambath Jaleel; Myra Wyckoff; Myra Wyckoff  
**Subject:** RE: FW: PEDIATRICS: Decision Letter for MS ID 2013-2023

It may be better to limit the study to centers that were part of GDB during both periods.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: (b)(6)

---

**From:** Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]

**Sent:** Thursday, September 05, 2013 1:06 PM

**To:** Luc Brion; Luc Brion

**Cc:** (b)(6)@gmail.com>; ; Wrage, Lisa Ann; Wrage, Lisa Ann; <nfiner@ucsd.edu>; ; Wally Carlo, M.D.; Wally Carlo, M.D.; Roy Heyne; Roy Heyne; Gantz, Marie; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Das, Abhik; Gantz, Marie; Gantz, Marie; Mambarambath Jaleel; Mambarambath Jaleel; Myra Wyckoff; Myra Wyckoff

**Subject:** Re: FW: PEDIATRICS: Decision Letter for MS ID 2013-2023

Barbara J. Stoll, MD

J peds is fine. Wonder if pre post diff would be diff in centers that were not part of support-- reviewer comment ant excluding pts/ sites.

George W. Brumley, Jr., Professor and Chair

Department of Pediatrics, Emory University School of Medicine

Director, The Pediatric Center of Emory and Children's Healthcare of Atlanta

President, Emory-Children's Center

1760 Haygood Drive

Atlanta, GA 30322

Office: 404-727-2456 Fax: 404-727-5737

[bstoll@emory.edu](mailto:bstoll@emory.edu)

Confidential - Please do not forward.

**This message is for the designated recipient only and may contain**

---

UT Southwestern Medical Center  
The future of medicine, today.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News questions regarding RTI  
**Date:** Thursday, September 05, 2013 12:55:30 PM  
**Attachments:** [image001.png](#)

---

Bob:

How much funding does NIH provide to RTI – RTI gets a base award and study specific capitation each year – do we release this information? GMB would be the best to determine this.

with whom and how was data shared or sold regarding the SUPPORT study

Extended follow-up at school age for a cohort of children enrolled in SUPPORT is still ongoing, so data have not been shared outside the NRN

and, more generally, with whom and how is RTI data shared regarding other projects?

*From time-to-time, the NRN receives requests from non-Network researchers for protocol documents (protocol, manual, and forms) and study data for pre-specified purposes. All requests should be sent to the NICHD Program Scientist for consideration. Generally, data are not released until two years following publication of a primary study.*

*Depending on the nature of the request, it may go to the Data Access Subcommittee or directly to the Steering Committee. The Steering Committee votes to approve release of the requested information. The external requestor is asked to acknowledge the use of the NICHD Neonatal Research Network materials in all relevant applications, presentations, and publications." Typically, the Steering Committee requires a scientific protocol with stated hypotheses, specific aims, background and significance and a reasonably detailed study design and analysis plan, as well as a budget to entertain such external requests.*

As per the data sharing plan proposed by the NRN Data Coordinating Center (DCC) and approved by NIH, if external data sharing is approved by the NRN Steering Committee and NICHD, the DCC will create de-identified limited-access data sets for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. Therefore, in order to protect the confidentiality and privacy of the subjects, external investigators granted access to these data must adhere to strict requirements defined by the NRN Steering Committee that are incorporated into a standard Data Distribution Agreement to which all external investigators seeking the data must agree to abide and adhere to. The Data Distribution Agreement may be subject to review by the legal departments and IRBs of the DCC and the NRN clinical centers, and must be approved by the Steering Committee. Finally, in accordance with NICHD policies, outside researchers will be required to submit an approval from their IRB for the proposed research.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH

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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 12:47 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

Please see below.

(b)(5)

I guess we should (b)(5)

(b)(5)

Sorry to have to ask you again, Rose. I should have taken the data acquisition procedure down when we talked.

We can't (b)(5)

(b)(5)

Thanks.

**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 12:41 PM  
**To:** Myles, Renate (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Gianelli, Diane M (OASH)  
**Subject:** FW: CBS News questions regarding RTI

See below.

**John Burklow**  
Associate Director for Communications and Public Liaison  
National Institutes of Health  
Building 1, Room 344  
(301) 496-4461 (phone)  
(301) 496-0017 (fax)  
[burklowj@od.nih.gov](mailto:burklowj@od.nih.gov)



**Celebration of Science at NIH:** watch how medical research saves lives and improves health

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 12:39 PM  
**To:** Burklow, John (NIH/OD) [E]; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'  
**Subject:** CBS News questions regarding RTI

John and Diane,

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Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Thursday, September 05, 2013 11:33 AM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
Sorry for the delay.

- NIH funds the data support RTI International provides for all studies conducted by the NICHD Neonatal Research Network.
- RTI's NIH funding information is publicly available from NIH.
- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
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**Subject:** RE: CBS News is trying to reach you

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Kim  
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202-457-4383 office  
(b)(6) cell  
[skaenk@cbsnews.com](mailto:skaenk@cbsnews.com)

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**Subject:** RE: CBS News is trying to reach you

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Lisa

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**Sent:** Wednesday, September 04, 2013 11:53 AM  
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**Subject:** RE: CBS News is trying to reach you

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Regards,

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CBS News Washington Bureau  
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(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

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**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM

**To: News**

**Subject: CBS News is trying to reach you**

**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim

Producer

CBS News Washington Bureau

202-457-4383 office

(b)(6) cell

[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, September 05, 2013 12:51 PM  
**To:** Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Yeah. I got John's earlier note. We're working on it. The short answer is that the data isn't sold, but there are criterion for making it available to researchers.

I'll be back in touch.

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 12:50 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Burklow, John (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: CBS News questions regarding RTI

And another question about RTI.

**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Thursday, September 05, 2013 12:48 PM  
**To:** 'Skeen, Kim'; Gianelli, Diane M (OASH)  
**Cc:** Spangenberg, Kami; 'Bistreich-Wolfe, Lisa'; Myles, Renate (NIH/OD) [E]  
**Subject:** RE: CBS News questions regarding RTI

Hi, Kim—We'll be back to you later.

Thanks,

John

**John Burklow**  
Associate Director for Communications and Public Liaison  
National Institutes of Health  
Building 1, Room 344  
(301) 496-4461 (phone)  
(301) 496-0017 (fax)  
[burklowj@od.nih.gov](mailto:burklowj@od.nih.gov)



**Celebration of Science at NIH:** *watch how medical research saves lives and improves health*

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Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

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- The data from the NICHD Neonatal Research Network are collectively owned by the Network steering committee. Questions about data sharing should be directed to the NICHD.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Thursday, September 05, 2013 11:23 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Lisa,

Just making sure you received this email from yesterday. We look forward to receiving your response. Thank you.

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Skeen, Kim  
**Sent:** Wednesday, September 04, 2013 3:09 PM  
**To:** 'Bistreich-Wolfe, Lisa'  
**Subject:** RE: CBS News is trying to reach you

Thank you! So with the cooperative agreement mechanism, are you saying all your finding comes exclusively from NIH— and also that no other clients or purchasers used the data, correct? (Again, for background, this is probably way out of what would ever be in the story we're working on, but) what is the amount of money you receive from NIH for this? Thank you very much!

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 3:02 PM  
**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
RTI is funded by NIH under a cooperative agreement mechanism to provide data support for all studies conducted by the NICHD Neonatal Research Network.

Lisa

---

**From:** Skeen, Kim [<mailto:SkeenK@cbsnews.com>]  
**Sent:** Wednesday, September 04, 2013 11:53 AM  
**To:** Bistreich-Wolfe, Lisa  
**Subject:** RE: CBS News is trying to reach you

Thanks Lisa: just for background, to understand RTI a little bit better, can you tell me where the payments for your services originated for this particular study (and how much it was)? Were all payments from NIH? And if so, do you know were there other sources of funding that gave to NIH for the study? Did any other clients purchase or use this data? Thank you!

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

---

**From:** Bistreich-Wolfe, Lisa [<mailto:lbistreich@rti.org>]  
**Sent:** Wednesday, September 04, 2013 11:24 AM

**To:** Skeen, Kim  
**Cc:** Spangenberg, Kami  
**Subject:** RE: CBS News is trying to reach you

Kim,  
I got your voicemail and email. RTI's role in the SUPPORT study is described here.

RTI International's Role in the NICHD Neonatal Network SUPPORT Study

- We are aware of concerns voiced about the informed consent document regarding this particular study.
- RTI serves as the data coordinating center for the Neonatal Network. As such, we have no clinical role in studies conducted by the network.
- As a data coordinating center, RTI did not draft or approve the informed consent for this study, nor did we play any role in enrolling or gaining the consent of study participants.

Thanks,  
Lisa

Lisa Bistreich-Wolfe  
Media Relations Manager  
RTI International  
919.316.3596  
[www.rti.org/newsroom](http://www.rti.org/newsroom)

---

**From:** Skeen, Kim[SMTP:SKEENK@CBSNEWS.COM]  
**Sent:** Tuesday, September 03, 2013 4:55:51 PM  
**To:** News  
**Subject:** CBS News is trying to reach you  
**Auto forwarded by a Rule**

Hi Lisa,

I just left a voicemail message at your office. CBS News is trying to reach you regarding RTI's role in the SUPPORT study on premature infants. Please give us a call at your earliest convenience. Thanks so much.

Regards,

Kim  
Producer  
CBS News Washington Bureau  
202-457-4383 office  
(b)(6) cell  
[skeenk@cbsnews.com](mailto:skeenk@cbsnews.com)

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (b)(6)@gmail.com; Wrage, Lisa Ann; Barbara Stoll; nfiner@ucsd.edu; Wally Carlo, M.D.; Roy Heyne; Gantz, Marie; Das, Abhik; Gantz, Marie; Mambarambath Jaleel; Myra Wyckoff  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PEDIATRICS: Decision Letter for MS ID 2013-2023  
**Date:** Thursday, September 05, 2013 10:33:53 AM

---

Will do! (b)(5) agrees..

Luc

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, September 05, 2013 7:47 AM  
**To:** Luc Brion; (b)(5)@gmail.com; Wrage, Lisa Ann; Barbara Stoll; nfiner@ucsd.edu; Wally Carlo, M.D.; Roy Heyne; Gantz, Marie; Das, Abhik; Gantz, Marie; Mambarambath Jaleel; Myra Wyckoff  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PEDIATRICS: Decision Letter for MS ID 2013-2023

I am fine with submission to JPEDS - the reviews are pretty good!

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

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

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
**Sent:** Thursday, September 05, 2013 7:04 AM  
**To:** (b)(6)@gmail.com; Wrage, Lisa Ann; Barbara Stoll; nfiner@ucsd.edu; Wally Carlo, M.D.; Roy Heyne; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Mambarambath Jaleel; Myra Wyckoff  
**Subject:** FW: PEDIATRICS: Decision Letter for MS ID 2013-2023

Jackie et al:

Sorry but the manuscript was not accepted by Pediatrics. Unless I missed something, comments from the reviewers appear rather minor.

I attach a revised version that includes corrections in response to all the comments (also attached) I have received after submission to Pediatrics. This week-end I will reformat this manuscript for Journal of Pediatrics, unless most of you tell me otherwise. If you prefer me to submit the manuscript to another journal please let me know by tomorrow.

Thanks a lot for your collaboration,

Best regards,

Luc

Luc P. Brion, MD  
Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern  
Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-9063  
Office: (214) 648-2835  
Fax: (214) 648-2481  
luc.brion@utsouthwestern.edu

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From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com  
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of  
PediatricsEditorial@aap.org  
Sent: Thursday, August 22, 2013 10:01 AM  
To: Luc Brion; lucbrion@gmail.com  
Subject: PEDIATRICS: Decision Letter for MS ID 2013-2023

22-Aug-2013

RE: MS ID 2013-2023

Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Dear Dr. Brion:

Thank you for submitting your manuscript to Pediatrics. We are sorry that we are not accepting it for publication. Because of the large number of submissions, the editors must reject many worthy manuscripts. Rejection reflects the priorities of the journal; it does not necessarily indicate that your manuscript is unsuitable for publication elsewhere.

Comments from our reviewers are included below. Reviewer input is one of several factors involved in making decisions on papers. Because of space limitations, even papers receiving positive comments from the reviewers are often rejected.

We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD  
Editor-in-Chief, Pediatrics  
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics,  
Vermont Children's Hospital at Fletcher Allen Health Care  
802-656-0027 (office)  
802-656-2077 (fax)  
lewis.first@uvm.edu

Page 1413 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

(b)(4),(b)(6)



---

UT Southwestern Medical Center  
The future of medicine, today.

**From:** Luc Brion  
**To:** [lucbrion@gmail.com](mailto:lucbrion@gmail.com); Wraga, Lisa Ann; Barbara Stoll; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Wally Carlo, M.D.; Roy Heyne; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie; Mambarambath Jaleel; Myra Wyckoff  
**Subject:** FW: PEDIATRICS: Decision Letter for MS ID 2013-2023  
**Date:** Thursday, September 05, 2013 7:03:59 AM  
**Attachments:** [Additional Review of Changes in Therapy and Outcomes Associated With the SUPPORT Trial Sent on Behalf of William E. Trucco.htm](#)  
[Jackie LeVan Manuscript NRN 09-05-13.doc](#)  
[Boilerplate, LeVan, Changes in Therapy Associated with SUPPORT, 2013-08-20.docx](#)

---

Jackie et al:

Sorry but the manuscript was not accepted by Pediatrics. Unless I missed something, comments from the reviewers appear rather minor.

I attach a revised version that includes corrections in response to all the comments (also attached) I have received after submission to Pediatrics. This week-end I will reformat this manuscript for Journal of Pediatrics, unless most of you tell me otherwise. If you prefer me to submit the manuscript to another journal please let me know by tomorrow.

Thanks a lot for your collaboration.

Best regards,

Luc

Luc P. Brion, MD  
Professor of Pediatrics  
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas  
5323 Harry Hines Boulevard, STOP 9063  
Dallas, TX 75390-9063  
Office: (214) 648-2835  
Fax: (214) 648-2481  
[luc.brion@utsouthwestern.edu](mailto:luc.brion@utsouthwestern.edu)

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[\[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com\]](mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com) On Behalf Of  
[PediatricsEditorial@aap.org](mailto:PediatricsEditorial@aap.org)  
Sent: Thursday, August 22, 2013 10:01 AM  
To: Luc Brion; [lucbrion@gmail.com](mailto:lucbrion@gmail.com)  
Subject: PEDIATRICS: Decision Letter for MS ID 2013-2023

22-Aug-2013

RE: MS ID 2013-2023

**Change in Practice After The Surfactant, Positive Pressure, and Oxygenation Randomized Trial**

Dear Dr. Brion:

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We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD  
Editor-in-Chief, Pediatrics  
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics,  
Vermont Children's Hospital at Fletcher Allen Health Care  
802-656-0027 (office)  
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lewis.first@uvm.edu

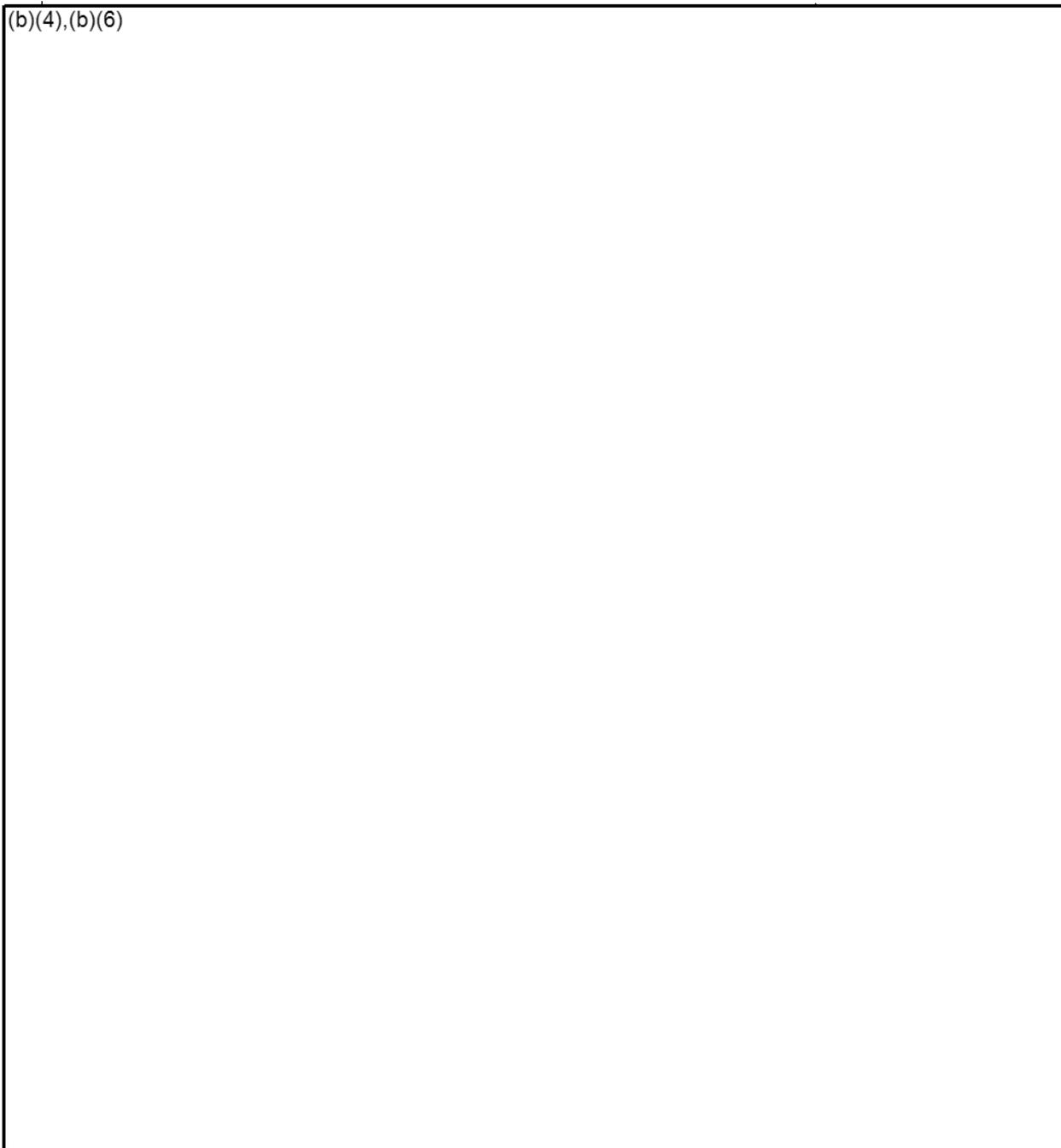
Reviewer: 1

(b)(4),(b)(6)

Reviewer: 2

(b)(4),(b)(6)

(b)(4),(b)(6)



---

UT Southwestern Medical Center  
The future of medicine, today.

**From:** Mcbrien, James, D [jdmcbrien@cmh.edu]  
**Sent:** Monday, July 01, 2013 8:21 AM  
**To:** Luc Brion  
**Cc:** Truog, William (MD); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** Additional Review of "Changes in Therapy and Outcomes Associated With the SUPPORT Trial" \*Sent on Behalf of William E. Truog\*

**Below is an additional review of the above referenced manuscript.**

Thanks,

Jim

.....  
LeVan and colleagues have performed an interesting and important evaluation of observational data to attempt to determine whether changes in practice have resulted in changes in outcomes among ELBW infants in the NRN. The logic and analysis of the study are clear and reasonable. The authors have appropriately acknowledged the difficulties of determining causality from observational data. I have several comments that may improve the manuscript; most of them are minor.

**Major Comments**

1. The authors have evaluated a clearly delimited set of primary (Table 2) and secondary (Table 3) outcomes that could be attributed to change in practice. They have also evaluated a large number of tertiary outcomes (Table 4), some of which are potentially intermediate measures of practice change (e.g. surfactant administration), but others of which are potential confounders or outcomes of practice change. It might be reasonable to specify and separate out the variables that might indicate practice change. This might help support the authors' contention that the results of SUPPORT influenced clinical practice. The intermediate outcomes that come to mind for the CPAP vs. surfactant aspect include surfactant administration, DR intubation and number of infants with 0 days on the ventilator, for instance. As the authors point out, intermediate outcomes for the saturation aspect are more difficult to identify. They might, however, include FiO2 measures, which changed in the opposite direction than might have been expected with infants being maintained at higher saturations. Overall, clearer organization of tertiary outcomes would make a clearer case for the argument that SUPPORT led to practice change led to outcome change.

**Minor Comments**

1. Eligibility and exclusion criteria (pg. 6). It is not necessary to list known malformations under both inclusion and exclusion criteria.
2. Primary outcome variables (pg. 7). The authors should specify the differences between GDB and SUPPORT definitions of BPD and ROP.

3. Cut-off for pre-SUPPORT DR intubations (pg. 8). Using the pre-SUPPORT proportion of intubations at Parkland seems to be an arbitrary (but not unreasonable) cut-off. Is there another way to justify the choice of cut-off?
4. Results (pg. 9). It is not necessary to repeat numbers, percentages and p values for the results in both the tables and in the text. It might be more useful to use the text to amplify the crucial results without repeating the details.
5. Tables. This is an extension of my major comment and the results comment. I am grateful for the authors presenting the data in detail. However, the large sample size allows the description of many differences (e.g. race/ethnicity) that are statistically significant, but are so small that they are unlikely to be clinically significant. The authors should provide the reader with some guidance.
6. Minor Table issues.
  - The titles of Tables 3 and 4 are identical – they should be more descriptive.
  - The Apgar items in Table 4 are duplicated.
  - The items with mean, SD and median in Table 4 should perhaps have their own descriptive footnote, listed in the appropriate rows – I was puzzled at the presentation until I got down to the fine print.
  - Footnote 4 in Table 4 contains jargon.
7. Figure 2. I'd suggest some arbitrary labeling (e.g. A, B, C...) of the centers on the X-axis.
8. I have made a few minor grammatical corrections on the attached copy of the manuscript.

Overall, this is an excellent and important manuscript. Some fairly minor modifications may make it clearer and better able to support the contentions of the authors.

Electronic mail from Children's Mercy Hospitals and Clinics. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to Children's Mercy Hospital's Information Security Officer via return electronic mail at [informationsecurityofficer@cmh.edu](mailto:informationsecurityofficer@cmh.edu) and expunge this communication without making any copies. Thank you for your cooperation.

## Changes in Therapy and Outcomes Associated with the SUPPORT Trial

Jaclyn M. LeVan, DO<sup>1,2</sup>; Luc P. Brion, MD<sup>1</sup>; Lisa A. Wrage, MPH<sup>3</sup>; Marie G. Gantz, PhD<sup>3</sup>; Myra H. Wyckoff, MD<sup>4</sup>; Pablo J. Sánchez, MD<sup>1</sup>; Roy J. Heyne, MD<sup>1</sup>; Mambarambath Jaleel, MD<sup>1</sup>; Neil N. Finer, MD<sup>4</sup>; Waldemar A. Carlo, MD<sup>5</sup>; Abhik Das, PhD<sup>6</sup>; Barbara J. Stoll, MD<sup>7</sup>; Rosemary D. Higgins, MD<sup>8</sup> for the NICHD Neonatal Research Network

### Disclosures

Coauthors should list any conflicts of interests relevant to this paper here.

### Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources, and the National Center for Advancing Translational Sciences provided grant support for the Neonatal Research Network's Generic Database Study. The content of the publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011); Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

<sup>1</sup> Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX

<sup>2</sup> Pediatrix Medical Group, San Antonio, TX

<sup>3</sup> Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

<sup>4</sup> Division of Neonatology, University of California at San Diego, San Diego, CA

<sup>5</sup> Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL

<sup>6</sup> Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC

<sup>7</sup> Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA

<sup>8</sup> *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

#### Comment [swa1]:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – Abbot R. Laptook, MD; William Oh, MD; Angelita M. Hensman, RNC-NIC BSN; Dawn Andrews, RN; Kristen Angela, RN.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Nancy S. Newman, BA RN; Arlene Zadell RN; Julie DiFiore, BS.

Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084, UL1 TR77) – Kurt Schibler, MD; Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Estelle E. Fischer, MHA MBA; Lenora Jackson, CRC; Jennifer Jennings, RN BSN; Kristin Kirker, CRC; Greg Muthig, BS; Sandra Wuertz, BSN.

Duke University School of Medicine, University Hospital, University of North Carolina, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, UL1 RR24128, M01 RR30, UL1 RR25747) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Matthew M. Laughon, MD MPH; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Kim Lutz; Joanne Finkle, RN JD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, M01 RR39, UL1 TR454) – Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD.

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Linda L. Wright, MD; Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750, UL1 TR6) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Dianne E. Herron, RN.

RTI International (U10 HD36790) – Dennis Wallace, PhD; Margaret Cunningham, BS CCRP; Jeanette O'Donnell Auman, BS; Jenna Gabrio, BS CCRP; Carolyn Petrie Huitema, MS CCRP; James W. Pickett II, BS; Kristin M. Zaterka-Baxter, RN BSN CCRP.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, M01 RR70, UL1 TR93) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Melinda S. Proud, RCP.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Charles R. Rosenfeld, MD; Walid A. Selhab, MD; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Melissa Martin, RN; Nancy A. Miller, RN; Lizette E. Torres, RN; Diana M Vasil, RNC-NIC; Lijun Chen, PhD RN; Araceli Solis, RRT; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Esther G. Akpa, RN BSN; Nora I. Alaniz, BS; Katrina Burson, RN BSN; Patricia Ann Orekoya, RN BSN; Susan E. Dieterich, PhD; Patricia W. Evans, MD; Claudia I. Franco, RNC MSN; Charles E. Green, PhD; Margarita Jiminez, MD MPH; Terri L. Major-Kincade, MD MPH; Anna E. Lis, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; M. Layne Poundstone, RN BSN; Peggy Robichaux, RN BSN; Saba Khan Siddiki, MD; Maegan C. Simmons, RN; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT(ASCP).

Wayne State University, University of Michigan, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; John Barks, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN, Geraldine Muran, RN BSN.

Change in Practice After  
The Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Jaelyn M LeVan, DO,<sup>1,2</sup> Luc P Brion, MD,<sup>1</sup> Lisa Wrage, MPH,<sup>3</sup> Marie Gantz, PhD,<sup>3</sup>  
Myra H Wyckoff, MD,<sup>1</sup> Pablo Sánchez, MD,<sup>1</sup> Roy Heyne, MD,<sup>1</sup>  
Mambarambath Jaleel,<sup>1</sup> MD, Neil Finer, MD,<sup>4</sup> Waldemar A. Carlo, MD,<sup>5</sup>  
Abhik Das, PhD,<sup>3</sup> Barbara Stoll, MD,<sup>6</sup> Rose Mary D. Higgins, MD,<sup>7</sup> on behalf of the  
Eunice Kennedy Shriver NICHD Neonatal Research Network, Bethesda, MD.

Affiliations: <sup>1</sup>Department of Pediatrics, University of Texas Southwestern, Dallas, TX; <sup>2</sup>Current affiliation: Pediatrix Medical Group, San Antonio, TX; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>4</sup>Division of Neonatology, University of California, San Diego, CA; <sup>5</sup>Division of Neonatology, University of Alabama, Birmingham, AL; <sup>6</sup>Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; <sup>7</sup>Eunice Kennedy Shriver National Institute of Child, Health and Human Development, NICHD Neonatal Research Network, Bethesda, MD.

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Address correspondence to: Luc P Brion, MD, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, STOP 9063, Dallas, TX 75390-9063; Office: (214) 648-3903; Fax: (214) 648-2481; email: luc.brion@utsouthwestern.edu

Short title: Clinical practice changes after SUPPORT

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure; DR, delivery room; ETI-Endotracheal Intubation. GA, gestational age; GDB, generic database; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NRN, Neonatal Research Network; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity; RR, relative risk; SUPPORT, Surfactant, Positive Pressure, and Oxygenation Randomized Trial

Key words: very preterm, endotracheal intubation, delivery room, bronchopulmonary dysplasia, retinopathy of prematurity, mortality

Funding source: NICHD

Financial Disclosure Statement: nothing to disclose

Conflict of Interest Statement: nothing to disclose

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What's known on This Subject: The NICHD-sponsored Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) showed that continuous positive airway pressure (CPAP) is an alternative to endotracheal intubation (ETI) for DR therapy in very preterm infants.

What This Study Adds: The proportion of ETI significantly decreased after the SUPPORT trial in NICHD centers that participated.

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### **Contributors' Statement Page**

**Jaelyn M LeVan:** Dr. LeVan designed the study, drafted the protocol and the initial manuscript, and approved the final manuscript as submitted.

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**Lisa Wrage:** Ms. Wrage edited the protocol, conducted the statistical analysis, edited the initial manuscript and approved the final manuscript as submitted.

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## Abstract

### Introduction

The NICHD Neonatal Research Network (NRN) conducted the SUPPORT trial, in which preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestational age (GA) were randomized to: (1) CPAP initiated in the DR or DR intubation with early surfactant administration; and (2) oxygen saturation targets of 85 to 89% or 91 to 95%. The objective of the current study was to compare medical care practices and neonatal outcomes before and after the publication of SUPPORT within the NICUs in the NRN centers.

### Methods:

This was a retrospective cohort study using the prospective NRN generic database. We included infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born before (2003-04) and after SUPPORT (2010-12) at 11 centers which participated in SUPPORT and were part of the NRN in 2003-11. We excluded infants with syndromes or major malformations and those who received only comfort care. The primary outcome was DR intubation. The most important secondary outcomes were bronchopulmonary dysplasia (BPD)/death at 36 weeks, severe retinopathy of prematurity (ROP)/death and death by discharge.

### Results:

After adjustment for baseline variables, the RRs (post vs. pre-SUPPORT) for DR intubation (adjusted RR 0.88, 95% CI 0.85-0.91), ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99) and death at discharge (adjusted RR 0.86, 95% CI 0.76-0.98) were significantly lower than one.

### Conclusions:

After adjustment for baseline variables infants 24<sup>0/7</sup>-27<sup>6/7</sup> weeks GA born at participating NRN Centers after publication of SUPPORT had significantly lower percentages of DR intubation, BPD/death, ROP/death and death at discharge compared to infants born before SUPPORT.

**Introduction:**

The Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks gestational age (GA) were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room (DR) and protocol-driven limited ventilation begun in the DR, or endotracheal intubation (ETI) with surfactant administration (within one hour of birth) followed by a conventional ventilation strategy, and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%.<sup>1,2</sup> From February 2005 through February 2009, 1316 infants were enrolled, including 565 in the lower GA stratum (24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks) and 751 in the higher stratum (26<sup>0/7</sup> weeks to 27<sup>6/7</sup> weeks).<sup>1,2</sup> The results of the SUPPORT trial were published in May 2010.<sup>1,2</sup> The risks of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups.<sup>1</sup> In the CPAP group, infants had a lower proportion of endotracheal intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day seven. Among infants with GA 24<sup>0/7</sup> weeks to 25<sup>6/7</sup> weeks, the risk of death during hospitalization and at 36 weeks was significantly lower in the CPAP group than in the surfactant group. There was also less use of epinephrine in the DR in the CPAP group than in the surfactant group. The risk of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) was not significantly different between the two oxygen

saturation target groups. However, the risk of death was higher and that of severe ROP was lower in the low saturation target group than in the high target group.

The objective of this study was to determine if publication of SUPPORT was temporally associated with changes in clinical practice, specifically in the proportion of preterm inborn infants intubated in the DR. We hypothesized that after SUPPORT there would be a lower proportion of ETI in the DR in preterm infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks compared to the period before SUPPORT. We speculated that the decrease in proportion of ETI in the DR in each center after SUPPORT would depend on the baseline proportion before the trial. In this study we also aimed to determine whether neonatal outcomes in preterm infants with GA between 24<sup>0/7</sup> and 27<sup>6/7</sup> weeks changed after SUPPORT. These included the composite of death or BPD, the composite of severe ROP or death before discharge from the hospital, and death before discharge. We also examined if publication of SUPPORT was followed by changes in several other neonatal processes of care and outcomes.

## **Methods**

### **Study Design**

This was a retrospective birth cohort analysis with before/after design. We extracted data from the NICHD Generic Database (GDB) (a registry of very low birth weight infants born alive in NRN centers) in one birth cohort of patients born before the initiation of the SUPPORT trial and in a second preterm cohort born after publication of the SUPPORT Trial. We included the eleven centers that participated in the SUPPORT trial and in the NRN during the cycles relevant to the two cohorts.

Study Population:

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012). Based on numbers entered in GDB in 2010, we expected to obtain about similar number of patients in both cohorts.

Eligibility and exclusion criteria:

Eligibility and exclusion criteria were similar but not identical to those used in SUPPORT.<sup>1,2</sup> Specifically, eligible infants were inborn at 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks at birth by best obstetrical estimate delivered at an NRN center participating in the SUPPORT trial and included in the GDB during the entire study period (2003-2012). Exclusion criteria for this analysis were: known malformations, respiratory support (1<sup>st</sup> cohort) or medical therapy (2<sup>nd</sup> cohort) withheld or withdrawn at any time prior to death < 12 hours.

Baseline variables

Neonatal and maternal characteristics included birth weight, gestational age, gender, race/ethnicity, prenatal steroid use (any type or betamethasone, any or full course), mode of delivery, multiple birth, prolonged rupture of membranes, maternal hypertension, diabetes, or antibiotic use before delivery.

Primary outcome variable:

The primary outcome variable was ETI in DR.

Secondary outcome variables:

The most important secondary outcomes included the composite of death or BPD (oxygen use at 36 weeks of postmenstrual age (PMA), the composite of severe ROP (defined as ROP surgery or retinal detachment) or death before discharge from the hospital, and death before discharge. The definitions of BPD and ROP for this study were based on those used in the GDB; they were similar but not identical to the primary outcome of the SUPPORT trial.

Tertiary ~~Other secondary outcomes included outcomes included practice such as use of surfactant, ventilation and CPAP, treatment of patent ductus arteriosus and feeding practice, and other outcomes (including potential confounders):~~ BPD, severe ROP and other ROP outcomes, death within 12 hours or by 36 weeks PMA, ~~surfactant use, DR~~ outcome, Apgar scores, temperature within 60 minutes of birth, pneumothorax, pulmonary hemorrhage, sepsis, intraventricular hemorrhage (IVH), oxygen supplementation, ~~ventilation and CPAP use,~~ patent ductus arteriosus, feeding and weight related variables, proven necrotizing enterocolitis (NEC) (stage II or greater, modified Bell's classification)<sup>5</sup> and length of hospital stay among survivors.

Statistical analysis

Variables of interest were compared by study group using chi-square tests for categorical variables, Wilcoxon tests for Apgar scores and skewed continuous variables, and Student t-tests for all other continuous variables. Robust Poisson regression models were used for dichotomous outcomes to obtain adjusted relative risks (RR) and 95% confidence intervals (CI). General linear models were used for continuous outcomes, to obtain

differences in means and 95% CI. All models included pre-specified prenatal covariates (based on the literature) shown to affect outcomes in very preterm infants (GA, antenatal corticosteroids, gender, singleton vs. multiple, birth weight by 100 g increment)<sup>6</sup> as well as additional covariates that were significantly different by study group ( $p < 0.10$ ) in the unadjusted tests, and that preceded the outcome. The models for primary outcome and all secondary outcomes, with the exception of BPD, included additional variables that preceded birth (race/ethnicity, cesarean section, rupture of membranes  $> 24$  hours, maternal hypertension, and maternal diabetes), but not postnatal variables to which some infants may not have been exposed before the outcome took place. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.<sup>7-16</sup> Since we did not adjust p value for multiple comparisons, all secondary analyses should be considered as exploratory. A Spearman correlation was used to assess whether the change in proportion of delivery room intubations from the first period (pre-SUPPORT) to the second period (post-SUPPORT) was higher in centers with higher proportion of intubation during the first period.

## **Results**

A total of 6,601 infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age were born during the study periods and included in the GDB: 2,998 in 2003-2004 and 3,603 in 2010-2012 (Figure 1). Of these, 1,999 infants were born in NRN centers not included in this study and an additional 361 were outborn, these infants were excluded. Of the remaining infants, 176

infants with known malformations, 123 infants who had respiratory or medical support withdrawn prior to death < 12 hours, and 93 infants whose ~~had missing~~ inclusion/exclusion information was missing in the GDB were excluded, leaving a total study population of 3,849 infants: 1,617 infants in the pre-SUPPORT group and 2,232 infants in the post-SUPPORT group.

The baseline maternal and neonatal characteristics of both groups are shown in Table 1. There was more antenatal steroid use (89.6% vs. 82.8%,  $p < 0.0001$ ), maternal hypertension (27.4% vs. 19.9%,  $p < 0.0001$ ), maternal diabetes (5.4% vs. 2.6%,  $p < 0.0001$ ), cesarean section delivery (66.3% vs. 62.1%,  $p = 0.0078$ ), and prolonged rupture of membranes (24.1% vs. 27.5%,  $p = 0.017$ ) in the post-SUPPORT group, and race/ethnic distribution was different from the pre-SUPPORT group.

For the primary outcome, unadjusted comparison showed a significant decrease in the proportion of DR ETI in the post-SUPPORT cohort (Table 2). The adjusted risk of DR ETI (adjusted RR 0.88, 95% CI 0.85-0.91) significantly decreased after publication of SUPPORT.

For the most important secondary outcomes, unadjusted comparison showed a significant decrease in the proportion of death or BPD, death or ROP, and death in the post-SUPPORT group (Table 3). The adjusted risk of BPD/death (adjusted RR 0.94, 95% CI 0.89-0.99), severe ROP/death (adjusted RR 0.81, 95% CI 0.73-0.89), and death before discharge (adjusted RR 0.86, 95% CI 0.76-0.98) significantly decreased after publication of SUPPORT. The adjusted risk of severe ROP (adjusted RR 0.63, 95% CI 0.52-0.77) and of death or mechanical ventilation at day of life seven (adjusted RR 0.90, 95% CI 0.84-0.97) were significantly lower in the post-SUPPORT group (Table 3). In contrast,

the risk of BPD (adjusted RR 1.04, 95% CI 0.97-1.1) and of death at 36 weeks (adjusted RR 0.88, 95% CI 0.76-1.00) were not significantly different between groups. The average number of ventilator days among survivors decreased by 4.7 days (95% CI 3.2, 6.1) after SUPPORT.

Additional unadjusted comparisons are shown in table 4. Several differences were observed between the two periods.

Figure 2 shows the proportion of infants intubated in the DR during the first and second study periods in all centers in the study. The correlation between the proportion of intubations in the DR during the first period and the change in proportion of intubations in the DR from the first to the second period was not significant (Spearman correlation coefficient -0.44,  $p=0.18$ ).

#### **Discussion:**

Infants 24<sup>0/7</sup> to 26<sup>6/7</sup> weeks GA born after publication of SUPPORT in the 11 centers participating in the trial had a lower proportion of DR ETI and risk of BPD or death, and ROP or death compared to those infants born before the initiation of the SUPPORT. Severe ROP and death or mechanical ventilation at day of life 7 were significantly decreased in the group of infants in the post-SUPPORT group. These findings contrast with previous published reports from the NICHD NRN, which failed to show any improvement in survival without major neonatal morbidity between 1995-96 and 1997-2002,<sup>18</sup> and between 2003 and 2007.<sup>19</sup> They are consistent with a recent review of deaths among extremely low birthweight infants enrolled in the GDB which showed a decrease in mortality between 2000-2003 and 2008-2011.<sup>20</sup> These findings suggest that the results

of SUPPORT trial influenced both clinical practice and patient outcomes at NRN study sites. These findings also support the significant impact that the results of a randomized controlled trial have on clinical practice management and patient outcomes. As in several previous NRN publications we found major differences across centers.

The strengths of this study include a large sample size, the use of a prospective database which limits incomplete/missing data and information bias, and the use of multivariate analysis to take into account differences in confounding variables between the two periods. Limitations of this study include the observational design, which introduces confounding variables and bias and prevents any cause-effect interpretation, and the before/after study design, which could introduce changes in patient population, and secular trends. Definitions used in this study for BPD and ROP were those included in GDB during the entire duration of the study period. They differed from those used in SUPPORT, i.e., physiological definition of BPD defined as the receipt of more than 30% supplemental oxygen at 36 weeks or the need for positive-pressure support or, in the case of infants requiring less than 30% oxygen, the need for any supplemental oxygen at 36 weeks after an attempt at withdrawal of oxygen; and severe ROP defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment, with examination continued until SUPPORT outcome was reached or resolution occurred.<sup>1,2</sup>

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This study only include a limited proportion of patients born in the NRN because we only included centers that participated in SUPPORT and remained in the NRN until the end of the study period, thereby allowing analysis of center-specific changes after SUPPORT. In this study we compared data before SUPPORT with data after SUPPORT and thus were unable to analyze whether the decrease in proportion of ETI already started during

SUPPORT or occurred after its publication. The proportion of ETI at Parkland Memorial Hospital decreased in non-enrolled patients during SUPPORT and before its publication,<sup>21</sup> more than in a comparable contemporaneous cohort in the Vermont Oxford Neonatal Network. Since the current study includes several outcome variables, it is likely that some differences reached a p value < 0.05 just by chance; thus p values are presented for informational purposes. These analyses should be considered as exploratory. Furthermore, the large sample size lead to the description of many statistical differences, some of which are unlikely to have clinical significance (e.g., race/ethnicity). It is possible that additional unknown biases or confounding variables, such as changes in personnel, could have affected the results. The GDB did not include information on the rationale used for various practices used for each patient in each center. We had hypothesized that the change in the proportion in ETI after SUPPORT would be greater in centers with high baseline ETI proportion; although the correlation did not reach significance, this may have resulted from the small number of centers included in this study. Some centers may have changed practice guidelines and providers may have changed their practice based on SUPPORT. Since oxygen saturation was not prospectively collected before and after SUPPORT, it is impossible to determine whether changes in severe ROP and changes in mortality after SUPPORT reported in the present study are related to changes in median or ranges of oxygen saturation. Center-specific practice guidelines and individual practice may have changed based on other studies, e.g., studies on antenatal steroids,<sup>22</sup> treatment and prophylaxis of patent ductus arteriosus,<sup>23-25</sup> synchronized nasal intermittent positive-pressure ventilation,<sup>26</sup> prevention of central line-associated bloodstream infections,<sup>27,28</sup> or nutrition.<sup>29</sup> DR practices, including oxygen

exposure and thermoregulation, may have changed based on new resuscitation literature and on the revised 2010 national resuscitation program of the American Academy of Pediatrics and American Heart Association.<sup>30</sup> Several processes of care such as prophylaxis of nosocomial infection or approach to diagnosis and treatment of patent ductus arteriosus may have changed based on results of other studies. This study did not address how generalizable the study results might be to centers that did not participate in SUPPORT. It is possible that institution of evidence-based changes (and associated improvement in outcomes) is that centers participating in SUPPORT might have been more likely to accept the validity of evidence generated by their own investigators and patients than other centers might be.

#### Conclusion

After adjustment for baseline variables, the proportion of DR ETI, ROP/death, BPD/death, and death before discharge for preterm neonates 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' GA born at Network Centers was lower following the publication of SUPPORT trial compared to a period before SUPPORT. The adjusted risk of severe ROP and of death or mechanical ventilation at day seven of life ~~seven~~ also was significantly lower. In contrast, the risk of death at 36 weeks PMA and of BPD did not change significantly. The average number of ventilator days among survivors was lower after SUPPORT.

Since this is an observational study, it is impossible to determine the relative contribution of the results of SUPPORT trial and other studies on changes in clinical practice and patient outcomes at NRN study sites. However, our findings support the potential impact

that the results of a randomized controlled trial may have on clinical practice management and patient outcomes.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator), Ms. Lisa A. Wrage, and Dr. Marie G. Gantz (DCC Statisticians) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011);

Richard A. Polin, MD, Division of Neonatology, College of Physicians and Surgeons, Columbia University, (2011-present).

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#### **Comment [swa1]:**

The first cohort includes preterm patients born during a 2-year period preceding the SUPPORT trial (from 1/1/2003-12/31/2004). The second cohort includes preterm patients born after publication of the SUPPORT trial (1/1/2010-12/31/2012).

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## Figure Legends

Figure 1. Flow diagram

Figure 2. Percent delivery room intubations by pre/post SUPPORT period for the eleven Neonatal Research Network Centers included in this study

**Table 1. Maternal and Neonatal Characteristics<sup>1</sup>**

Characteristic	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Birth weight (grams); mean (SD)	825 (191)	818 (194)	0.32
Gestational Age (weeks)	25.7 (1.1)	25.7 (1.1)	0.93
% Male	858 (53.1)	1126(50.5)	0.11
Race/ethnicity:			
Non Hispanic Black	727 (45.0)	965/2192 (44.0)	0.02
Non Hispanic White	603 (37.3)	808/2192 (36.9)	
Hispanic	241 (14.9)	314/2192(14.3)	
Other	46 (2.8)	105/2192 (4.8)	
Antenatal Steroids: any type	1338/1616 (82.8)	1994/2225 (89.6)	<.0001
Antenatal Steroids: betamethasone	953/1614(59.1)	1980/2229(88.8)	<.0001
Multiple birth	370 (22.9)	540/2228 (24.2)	0.33
Mode of delivery: cesarean section	1004 (62.1)	1476/2228 (66.3)	0.008
Prolonged rupture of membranes: (> 24 hours)	436/1586 (27.5)	520/2161 (24.1)	0.017
Maternal hypertension	322 (19.9)	610/2230 (27.4)	<0.0001
Maternal diabetes	42 (2.6)	120 /2231 (5.4)	<0.0001
Maternal Antibiotics	1198/1615 (74.2)	1618/2228 (72.6)	0.28

<sup>1</sup> presented as mean (SD) for continuous variables, and n (%) for categorical variables.

<sup>2</sup> The p-values shown are from Student t-tests for continuous variables and chi-square tests for categorical variables.

**Table 2. Primary Outcome<sup>1</sup>**

<b>Outcome</b>	<b>Pre-SUPPORT N=1617</b>	<b>Post-SUPPORT N=2232</b>	<b>p-value<sup>2</sup></b>	<b>Adjusted RR<sup>3</sup> (95% CI)</b>	<b>Adjusted p-value<sup>3</sup></b>
Intubated in delivery room	1313 (81.2)	1539 (69.0)	<0.0001	0.88 (0.85-0.91)	<0.0001

Abbreviation: RR, relative risk

<sup>1</sup> presented as n (%)

<sup>2</sup> unadjusted p-value from Chi-Square tests

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson model taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center

<sup>4</sup> adjusted p-values from robust Poisson model

**Table 3. Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>	Difference in Means <sup>3</sup> (95% CI)	adjusted RR <sup>3</sup> (95% CI)	Adjusted p value <sup>4</sup>
BPD or death at 36 weeks	970 (60.0)	1199/2213 (54.2)	0.0003	-	0.94 (0.89-0.99)	0.02
Severe ROP or death	515/1581 (32.6)	559/2165 (25.8)	<0.0001	-	0.81 (0.73-0.89)	<0.0001
Death before discharge	358/1614 (22.2)	393/2196 (17.9)	0.001	-	0.86 (0.76-0.98)	0.02
Bronchopulmonary dysplasia	664/1311 (50.7)	855/1869 (45.8)	0.0064	-	1.04 (0.97-1.1)	0.26
Severe retinopathy of prematurity	174/1294 (13.5)	181/1873 (9.7)	0.0009	-	0.63 (0.52-0.77)	<0.0001
Death by 36 weeks	306 (18.9)	344/2222 (15.5)	0.0050	-	0.88 (0.76-1.00)	0.06
Death or mechanical ventilation on day 7	741/1613 (45.9)	875/2211 (39.6)	<0.0001	-	0.90 (0.84-0.97)	0.0033
Days on ventilator (survivors) <sup>4</sup>	22.3 (24.4), 13	17.8 (21.3), 9.0	<0.0001	-4.7 (-6.1, -3.2)		<0.0001

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; RR, relative risk  
<sup>1</sup> presented as mean (SD), median for days on ventilator and n (%) for categorical variables.

<sup>2</sup> unadjusted p-values from Chi Square tests, or Wilcoxon tests, as appropriate

<sup>3</sup> adjusted RRs (Post vs. Pre SUPPORT) from robust Poisson models taking into account gestational age, birth weight (by 100 g increment), antenatal corticosteroids, gender, singleton vs. multiple, race/ethnicity, cesarean section, rupture of membranes > 24 hours, maternal hypertension, maternal diabetes, and Neonatal Research Network center. The model for BPD contained these same additional variables as well as intubation in the DR, surfactant, FiO<sub>2</sub> at 24 hours, patent ductus arteriosus (PDA) ligation, PDA indomethacin treatment, late onset sepsis and intrauterine growth restriction.

<sup>4</sup> adjusted p-values from robust Poisson models (categorical variables) or general linear models (continuous variable).

**Table 4. Tertiary Secondary Outcomes<sup>1</sup>**

Outcome	Pre-SUPPORT N=1617	Post-SUPPORT N=2232	p-value <sup>2</sup>
Delivery room oxygen	1604 (99.2)	2167(97.1)	<0.0001
Delivery room bag & mask ventilation	1352/1616 (83.7)	1742/2231 (78.1)	<0.0001
Delivery room chest compressions	123 (7.6)	173 (7.8)	0.87
Delivery room administration of medication <sup>3</sup>	89 (5.5)	84 (3.8)	0.0101
Apgar score, 1 min., median (IQR)	4 (2-6)	4 (2-6)	<0.0001
n/N (%) < 3	454/1612 (28.2)	842/2224 (37.9)	<0.0001
Apgar score, 5 min., median (IQR)	7 (6-8)	7 (5-8)	0.0007
n/N (%) < 3	94/1613 (5.8)	187/2226 (8.4)	0.0025
Apgar score, 1 min.	4 (2-6)	4 (2-6)	<0.0001
Apgar score, 5 min.	7 (6-8)	7 (5-8)	0.0007
Temperature within 60 min of birth	35.7 (1.1)	36.5 (0.8)	<0.0001
Surfactant	1427 (88.3)	1846/2222 (83.1)	<0.0001
Death < 12 hours	14 (0.9)	29 (1.3)	0.20
Fractional inspiratory oxygen concentration at 24 hours	0.34 (0.19), 0.26	0.31 (0.15), 0.25	0.0010
Fractional inspiratory oxygen concentration >0.90 at 24 hours	82/1574 (5.2)	57/2163 (2.6)	<0.0001
Pneumothorax	135/1604 (8.4)	121/2204 (5.5)	0.0004
Pulmonary hemorrhage	181/1603 (11.3)	150/2204 (6.8)	<0.0001
Postnatal Steroids	195/1599 (12.2)	268/2155 (12.4)	0.82
Days on Supplemental oxygen (survivors) <sup>4</sup>	59.2 (36)	56.6 (37.5)	0.06
Days on continuous positive airway pressure (survivors) <sup>4</sup>	16.5 (14.3), 13	18.8 (15.8), 16	0.0005
Retinopathy of prematurity: Stage 3 or worse	238/1295 (18.4)	251/1875 (13.4)	0.0001
Retinopathy of prematurity: Plus disease	172/1280 (13.4)	149/1875 (8.0)	<0.0001
Retinopathy of prematurity: Intervention	172/1288 (13.4)	171/1873 (9.1)	0.0002
Patent ductus arteriosus	795/1604 (49.6)	984/2203 (44.7)	0.0028
Patent ductus arteriosus, indomethacin	587/1604 (36.6)	473/2203 (21.5)	<0.0001
Patent ductus arteriosus, indomethacin or ibuprofen	587/1604 (36.6)	603/2203 (27.4)	<0.0001
Patent ductus arteriosus ligation	226/1604 (14.1)	186/2203 (8.4)	<0.0001
Severe intraventricular hemorrhage	288/1555 (18.5)	300/2147 (14.0)	0.0002
Early onset sepsis	38/1604 (2.4)	41/2194 (1.9)	0.29
Late onset sepsis	623/1533 (40.6)	503/2120 (23.7)	<0.0001
First day full feeds	27.2 (17.1), 22	24 (14.3), 20	<0.0001
Proven necrotizing enterocolitis	177 (11.0)	209 (9.5)	0.13
Weight at 36 weeks postmenstrual age	2031 (432)	2134 (399)	<0.0001
Weight at discharge	2857 (848), 2630	3104 (886), 2963	<0.0001
Length of hospital stay (days) (survivors)	84.4 (51.5), 83	90.3 (52), 90	<0.0001

Abbreviation: IQR, interquartile range

<sup>1</sup>presented as mean (SD), median for days on ventilator, continuous positive airway pressure, fractional inspiratory oxygen concentration at 24 hours, days of life at which full feeds were achieved, weight at discharge, and length of hospital stay; median (interquartile range) for Apgar scores; mean (SD) for all other continuous variables, and n (%) for categorical variables.

<sup>2</sup>unadjusted p-values from Chi Square tests, Student t-tests, or Wilcoxon tests, as appropriate

<sup>3</sup>The definition of medications administered in the delivery room was limited to epinephrine for the second period.

<sup>4</sup>survivors to discharge or 120 days, whichever came first, max is 120 days.

Figure 1

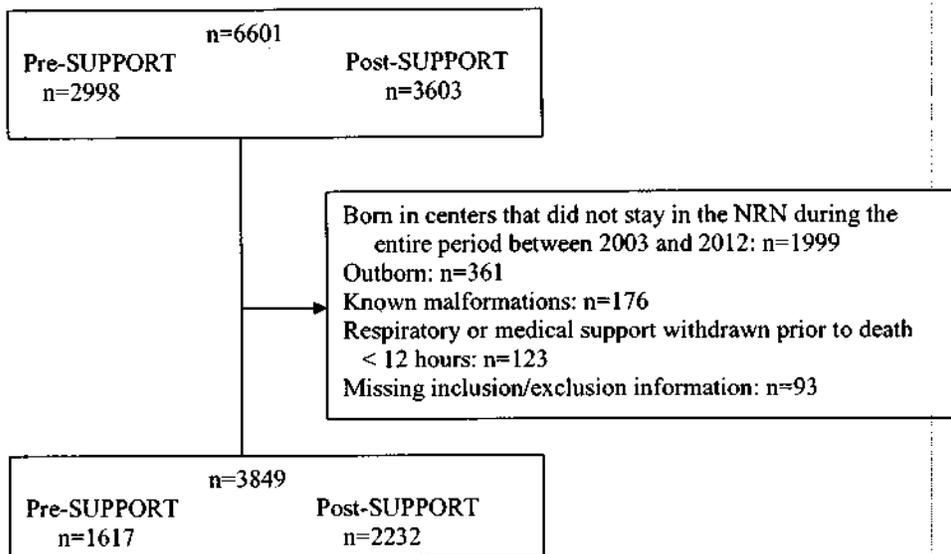
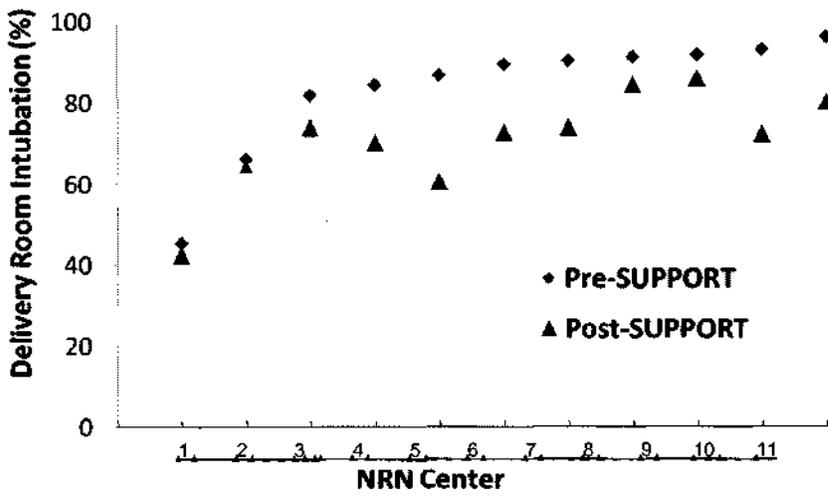


Figure 2



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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Clearance | Ambal, Association of PaCO2 with outcomes in SUPPORT  
**Date:** Wednesday, September 04, 2013 2:43:05 PM

---

Put it in track 2 so folks take note - indicate that it is a secondary analysis of SUPPORT Trial data

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, September 04, 2013 2:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Clearance | Ambal, Association of PaCO2 with outcomes in SUPPORT

Any reason this should go through Track 2?

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** Re: Science magazine query - re SUPPORT issue  
**Date:** Thursday, August 29, 2013 3:03:22 PM

---

I can come

Sent from my iPhone

On Aug 29, 2013, at 2:49 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)> wrote:

If easy; otherwise, don't bother, I think you have given me complete info.

Alan E. Guttmacher, M.D.  
Director  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
National Institutes of Health  
31 Center Drive  
Building 31, Room 2A03  
Bethesda, MD 20892-2425

Phone: 301-496-3454  
e-mail: [guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)  
url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 2:49 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** RE: Science magazine query - re SUPPORT issue

Would you like me to come over?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research  
Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 2:48 PM

**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Science magazine query - re SUPPORT issue

Because of what sounds (b)(6) es, he will call me back at 3:30, instead.

Alan

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 2:00 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** FW: Science magazine query - re SUPPORT issue

Do you want to call him? Or have him call you?

**From:** (b)(6)  
**Sent:** Thursday, August 29, 2013 1:59 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Science magazine query - re SUPPORT issue

great. do you want to call me at 2:45? my number is (b)(6)

Thanks!

Arthur Allen  
freelance writer, Washington DC  
author, *Vaccine: the Controversial Story of Medicine's Greatest Lifesaver* (WW Norton, 2007); *Ripe: The Search for the Perfect Tomato* (Counterpoint, 2010)

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

**From:** Bock, Robert (NIH/NICHD) [E] (NIH/NICHD) [E] <bockr@exchange.nih.gov>  
**To:** (b)(6)  
**Cc:** Guttmacher, Alan (NIH/NICHD) [E] (NIH/NICHD) [E] <guttmach@mail.nih.gov>  
**Sent:** Thu, Aug 29, 2013 1:53 pm  
**Subject:** RE: Science magazine query - re SUPPORT issue

Yes. Dr. Guttmacher is free today from 2:45-3:00 or from 3:45-4:45.

Thanks.  
Bob

**From:** (b)(6)  
**Sent:** Thursday, August 29, 2013 1:51 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Science magazine query - re SUPPORT issue

sorry I missed your call. Yes, Dr. Guttmacher would be great. let me know when. I have an appointment sent for 4 pm eastern, otherwise am pretty free.

Arthur Allen  
freelance writer, Washington DC  
author, *Vaccine: the Controversial Story of Medicine's Greatest Lifesaver* (WW Norton, 2007); *Ripe: The Search for the Perfect Tomato* (Counterpoint, 2010)

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

From: Bock, Robert (NIH/NICHD) IE1 (NIH/NICHD) IE1 <bockr@exchange.nih.gov>

To: (b)(6)

Sent: Thu, Aug 29, 2013 1:09 pm

Subject: RE: Science magazine query - re SUPPORT issue

**Hi Mr. Allen. I left a voice mail for you earlier. Are you still interested in speaking with someone about the SUPPORT trial?**

**Per my voice mail, I don't think we can get Dr. Higgins, but our institute director, Dr. Alan Guttmacher, has some openings this afternoon.**

**Please let us know.**

**Thanks**

**Bob Bock  
Press Officer  
NICHD  
301-496-5134**

From: (b)(6)

Date: August 28, 2013, 7:36:41 PM EDT

To: <rh298n@nih.gov>

Subject: Science magazine query - re SUPPORT issue

Dear Dr. Higgins,

I attended the hearing at HHS today that stemmed from the SUPPORT controversy and spoke with your colleague Kathy Hudson, who is an old friend. She recommended I speak with you. I am trying to find out what impact this brouhaha is having on neonate studies funded by NIH. Please feel free to send this by your PAO officer if need be. I'm in a bit of a rush though - I need to write the story tomorrow (Thursday)

Thanks and best wishes

Arthur Allen  
freelance writer, Washington DC  
author, *Vaccine: the Controversial Story of Medicine's Greatest Lifesaver* (WW Norton, 2007); *Ripe: The Search for the Perfect Tomato* (Counterpoint, 2010)

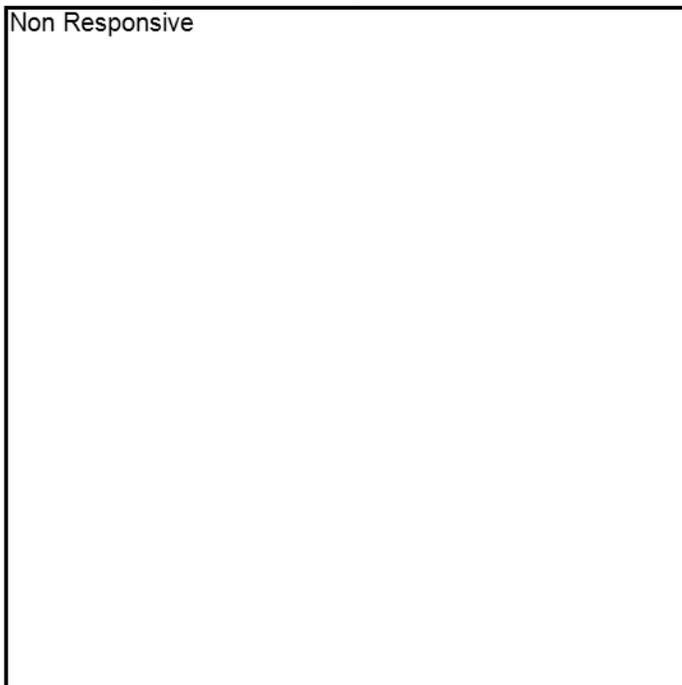
**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A  
**Date:** Thursday, August 29, 2013 2:47:02 PM

---

This is information that the sites have provided so I guess (b)(5) perhaps listing the number of sites that have gone back to their IRBs and halted. If we didn't list the site, they remain recruiting. Here is the real time update of recruiting as of today:

**TOP Trial Randomization Summary Report**  
**Report Date: Aug-29-2013 14:46<sup>1</sup>**

Non Responsive



Rosemary D. Higgins, MD  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 2:44 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]

**Subject:** RE: Updated support Q and A

Am I at liberty to (b)(5)

The sites you did not list – is that because (b)(5)

(b)(5)

Alan E. Guttmacher, M.D.  
Director  
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National Institutes of Health  
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Phone: 301-496-3454  
e-mail: [gutmach@mail.nih.gov](mailto:gutmach@mail.nih.gov)  
url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 12:49 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

I think he might also ask whether (b)(5)

(b)(5)

Answer: ????

And what other trials are currently ongoing on the NRN?

Alan

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 12:27 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

I added a few very minor comments.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 12:19 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

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I've amended the Support Q and A per below, to include the (b)(5) [REDACTED]  
[REDACTED]

Please let me know if you need anything else.

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**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 10:50 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

Can we add stuff about 1) (b)(5) [REDACTED] and 2) (b)(5) [REDACTED] specifically?

Alan E. Guttmacher, M.D.  
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**Cc:** Childress, Kerri (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Updated support Q and A

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**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A  
**Date:** Thursday, August 29, 2013 12:55:16 PM  
**Attachments:** Current studies and suspension.docx

Here is a document I did for Kathy Hudson in the last two weeks – the site suspensions are listed after the verbiage on the ongoing trials. Of note, [Non Responsive]  
[Non Responsive]

Let me know if you need additional information

Rose

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**Sent:** Thursday, August 29, 2013 12:49 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

I think he might also ask [b)(5)]

[b)(5)]

Answer: ????

And what other trials are currently ongoing on the NRN?

Alan

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 12:27 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Gutmacher, Alan (NIH/NICHD) [E]  
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**Cc:** Childress, Kerri (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Updated support Q and A

Please see attached, fyi.

#### Current studies:

**NEST: A Multi-center Randomized Trial of Laparotomy vs. Drainage as the Initial Surgical Therapy for ELBW Infants with Necrotizing Enterocolitis (NEC) or Isolated Intestinal Perforation (IP): Outcomes at 18-22 months Adjusted Age.** Short title: Necrotizing Enterocolitis Surgical Trial (NEST).

This trial will compare the effectiveness of two commonly employed surgical procedures - laparotomy versus peritoneal drainage - commonly used to treat necrotizing enterocolitis (NEC) or isolated intestinal perforations (IP) in extremely low birth weight infants ( $\leq 1,000$  g). Infants diagnosed with NEC or IP requiring surgical intervention, will be recruited. Subjects will be randomized to receive either a laparotomy or peritoneal drainage. Primary outcome is neurodevelopmental impairment-free survival at 18-22 months corrected age.

**MILK: Donor Milk versus Formula in Extremely Low Birth Weight (ELBW) Infants.** Short title: Milk Study.

The Milk Trial seeks to determine the effect on neurodevelopmental outcomes at age 22-26 months of donor human milk as compared to preterm infant formula as the in-hospital diet for infants whose mothers choose not to provide breast milk or are able to provide only a minimal amount. Infants will be randomized to receive donor breast milk or formula during their hospital stay. Infants will be followed until they reach 22-26 months of age.

#### Transfusion of Prematures (**TOP**) Trial

The objective of the TOP trial is to determine whether higher hemoglobin thresholds for transfusing ELBW infants resulting in higher hemoglobin levels lead to improvement in the primary outcome of neurodevelopmental impairment (NDI) -free survival at 22-26 months of age, using standardized assessments by Bayley. Long-term outcomes of extremely low birth weight (ELBW) preterm infants, those weighing less than 1000 g at birth, are poor and pose a major health care burden. Virtually all of these infants are transfused, but at inconsistent hemoglobin (Hgb) thresholds. It is currently unknown which transfusion strategy is superior.

**Hydrocortisone for BPD: Randomized Controlled Trial of the Effect Of Hydrocortisone on Survival Without Bronchopulmonary Dysplasia and on Neurodevelopmental Outcomes at 22 - 26 Months of Age in Intubated Infants < 30 Weeks Gestation Age.**

The Hydrocortisone and Extubation study will test the safety and efficacy of a 10 day course of hydrocortisone for infants who are less than 30 weeks estimated gestational age and who are intubated at 14-28 days of life. Infants will be randomized to receive hydrocortisone or placebo. This study will determine if hydrocortisone improves infants' survival without moderate or severe BPD and will be associated with improvement in survival without moderate or severe neurodevelopmental impairment at 22 - 26 months corrected age. FDA granted an exemption from an IND on July 1, 2010 .

**Late Hypothermia: Late Hypothermia for Hypoxic Ischemic Encephalopathy**

This study is a randomized, placebo-controlled, clinical trial to evaluate whether induced whole-body hypothermia initiated between 6-24 hours of age and continued for 96 hours in infants  $\geq$  36 weeks gestational age with hypoxic-ischemic encephalopathy will reduce the incidence of death or disability at 18-24 months of age. The study will enroll infants with signs of hypoxic-ischemic encephalopathy, and randomly assign them to either receive hypothermia or participate in a non-cooled control group.

**OC Trial: Optimizing (Longer, Deeper) Cooling for Neonatal Hypoxic-Ischemic Encephalopathy(HIE)**

The Optimizing Cooling trial will compare four whole-body cooling treatments for infants born at 36 weeks gestational age or later with hypoxic-ischemic encephalopathy: (1) cooling for 72 hours to 33.5°C; (2) cooling for 120 hours to 33.5°C; (3) cooling for 72 hours to 32.0°C; and (4) cooling for 120 hours to 32.0°C. The objective of this study is to evaluate whether whole-body cooling initiated at less than 6 hours of age and continued for 120 hours and/or a depth at 32.0°C in will reduce death and disability at 18-22 months corrected age.

## Studies temporarily halted or suspended following SUPPORT publicity

### **University of Alabama at Birmingham**

UAB temporarily suspended enrollment in all ongoing NRN trials (6 total) on May 23, 2013 to re-evaluate all of the IRB-approved consent forms in current use in each study. The following is a list of the dates the studies resumed screening:

MILK – July 29, 2013

Hydrocortisone and BPD – July 29, 2013

NEST – August 7, 2013

Optimizing Cooling – still in review

Late Hypothermia – still in review

TOP – still in review

### **Case Western Reserve University**

TOP – halted recruited on May 11, 2013 to re-evaluate IRB-approved consent form; resumed screening on June 6, 2013

### **Emory University**

TOP – Received IRB approval, and decided to halt screening on April 15, 2013 to re-evaluate consent form; resumed screening on July 29, 2013.

### **University of Iowa**

Satellite site at Mercy Hospital in Des Moines halted all recruitment in April 2013 to re-evaluate IRB-approved consent forms; five of 6 studies (excluding TOP) were restarted on June 18, 2013. TOP is still pending.

### **Children's Hospital of Philadelphia (University of Pennsylvania)**

TOP – halted recruitment in TOP on May 28, 2013 to re-evaluate IRB-approved consent form; resumed screening on May 31, 2013

### **University of Rochester**

TOP – halted recruited on April 24, 2013 to re-evaluate IRB-approved consent form; resumed screening on May 3, 2013

Satellite site at SUNY Buffalo – halted recruitment on April 19, 2013 in all 6 studies to re-evaluate IRB-approved consent form; resumed screening on May 2, 2013.

**University of Missouri (Children's Mercy Medical Center)** – halted screening in TOP on July 2, 2013 to re-evaluate IRB-approved consent form; resumed screening on August 16, 2013.

**UCLA** – IRB halted TOP screening on August 26 following Public Citizen's letter to Dr. Sebelius to re-evaluate IRB-approved consent form. The site anticipates amending the consent form.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Guttmacher, Alan \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Hudson, Kathy \(NIH/OD\) \[E\]](#)  
**Subject:** RE: More Press About OHRP meeting  
**Date:** Thursday, August 29, 2013 12:39:03 PM

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No NRN parent advisory group. Some sites may have parent groups (advisory/support etc), but I don't have these details.

Rose

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**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 12:38 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Hudson, Kathy (NIH/OD) [E]  
**Subject:** FW: More Press About OHRP meeting

Rose – Do they?

Alan

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Thursday, August 29, 2013 12:35 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** RE: More Press About OHRP meeting

One more thing: new zealand has a patient or parent's advisory group. Does the nrn have such a thing? Do the individual sites?

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A  
**Date:** Thursday, August 29, 2013 12:34:14 PM

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Ok

Let me know the time and I can try to come over

Rose

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Nice idea if the scheduling all works

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I almost forgot—Rose has offered to come to your office during the call, if you like.

---

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**Sent:** Thursday, August 29, 2013 10:42 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Updated support Q and A

Please see attached, fyi.

### **What is the SUPPORT Study?**

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) study was a large clinical trial that sought to determine how best to deliver oxygen to very small preterm infants and determine the ideal oxygen saturation targets for these very fragile newborns. The study compared the traditional means of providing oxygen, ventilator therapy with surfactant, to continuous positive airway pressure (CPAP), in which air is blown through a preterm infant's nostrils to gently inflate the lungs. When the study began, the standard treatment was to maintain oxygen levels in the range of 85 to 95 percent. The researchers sought to identify within this standard range the percentage of oxygen saturation that would minimize the risk of retinopathy of prematurity. Previous studies had shown that prolonged exposure to high levels of oxygen could increase the risk of retinopathy of prematurity, a complication of oxygen therapy that affects the retina and can sometimes result in vision loss. The study was divided into two arms, each of which proceeded at the same time, in the same group of infants. In the first arm, each infant had a 50 percent chance of receiving higher oxygen target saturation levels, and a 50 percent chance of receiving lower levels. In the second arm, each infant had a 50 percent chance of receiving oxygen by CPAP and a 50 percent chance of being assigned to the ventilator group.

### **What did the SUPPORT Study find?**

The researchers found that the higher range increased the chances of survival but also increased the chances for ROP. This unexpected but critical finding informed clinical practice. The researchers also concluded that CPAP therapy was as effective as ventilator therapy, and resulted in fewer complications.

### **How did mortality rates from the study compare to those of infants not in the study?**

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

#### *Percent Mortality (Unadjusted data):*

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

### **Had the researchers anticipated a lower survival rate for the infants in the lower oxygen range?**

No. The finding of a lower survival rate for those at the lower range was not anticipated or expected. At the time of the study, clinical practice for providing oxygen to very preterm babies varied widely. A target range of 85-95 percent was generally standard clinical practice and in 2007 was recommended by the American Academy of Pediatrics. In fact, at the time, emerging research showed that providing oxygen at the lower end of the acceptable range reduced the

risk of retinopathy without increasing the risk of death and neurodevelopmental impairment. As a result, physicians were starting to use the lower oxygen range to treat very preterm babies.

**Has the Office for Human Research Protections (OHRP) criticized the design or rationale for the study?**

It is critical to note that the treatments or the rationale of the study has never been in question by the Office for Human Research Protections.

**What had OHRP objected to?**

The OHRP cited the study for not including language, specifically in the risk/benefit section of the consent form, about research conducted in the 1950s suggesting the risk of death was higher with oxygen restriction.

**Why had the researchers not included this language?**

The older ROP studies were conducted before the widespread use of ventilators, pulse oximetry, and other sophisticated oxygen monitoring and measurement devices. The risk/benefit description under the oxygen saturation section of the consent form included language that reflected the available information/knowledge/data the oxygen administered at the lower saturation range reduced the risk of retinopathy. Since the current research had not shown a higher risk of death and neurodevelopmental impairment at any of these saturation levels (85-95%), the study authors did not list death and neurodevelopmental impairment as potential risks.

**Were parents adequately informed of the study risks?**

In addition to the consent form, representatives of the study explained the purpose of the research and its potential risks and benefits to parents and responded to their questions and concerns.

**Has the OHRP expressed any additional concerns with the study?**

In an interview with the New York Times (but not in the original letter to the Principal Investigator's institution, the University of Alabama), the Director of OHRP, Jerry Menikoff said: "Based on their very hypothesis, they were thinking that there might well be a difference... Being in the higher end [of the oxygen saturation range] should have put you at greater risk of developing eye disease." The parents were informed in the consent form that their children would be assigned at random to the higher or lower range. They were also told that they believed children at the lower range would be less likely to develop ROP. However, it was not explicitly stated that children at the higher range might be more likely to develop ROP.

OHRP has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care.

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There is currently a difference in scientific view between OHRP and NIH (NEJM Hudson, Guttmacher, Collins) with respect to the reasonable foreseeable risks at the time the study was begun.

**In addition to the consent form, were there any other safeguards to ensure that the infants would receive the optimal care?**

Attending physicians were allowed to override the settings if they thought their patients were in danger, and provide either more or less oxygen if they thought that following either course was in their patients' best interest. In addition, attending physicians and parents were free to ask that their children be withdrawn from the study at any time.

**What is the purpose of the Neonatal Research Network (NRN)?**

The NRN, which is currently composed of 18 medical research institutions, was established in 1986 to conduct clinical trials and observational studies in neonatal medicine to help reduce infant morbidity and mortality, and promote healthy outcomes.

Consistent with this mission, between 2000 and 2009, deaths of preterm infants declined 5.5%, from 109.75 per 1,000 live births to 103.48. Death rates for "early" preterm infants, those born before 32 weeks, declined 4.9% from 180.95 to 172.15 per 1,000 live births. In addition, NRN findings have helped to change clinical practice and improve outcomes for premature infants, such as:

- ✓ Identifying a safe way to protect newborns whose brains were getting insufficient oxygen
- ✓ Showing that providing additional Vitamin A to infants under 1,000 grams significantly reduced their risk of death or getting chronic lung disease
- ✓ Showing that giving intravenous immune globulin to reduce hospital-acquired infections in very low birthweight infants, actually increased rates of an often fatal intestinal condition in newborns
- ✓ Showing that giving additional glutamine, an amino acid, to extremely low birthweight infants did not reduce their risk of death or sepsis

**What are the implications of the SUPPORT study findings?**

The SUPPORT findings have already begun to change clinical practice. Based on the study findings, the American Academy of Pediatrics has begun developing guidelines on the use of non-invasive ways to administer oxygen to premature infants starting at birth. In addition, preliminary trends indicate that physicians treating very premature infants are using higher saturation rates to improve overall outcomes for these fragile infants.

**What are the implications of the SUPPORT study findings?**

The SUPPORT findings have already begun to change clinical practice. Based on the study findings, the American Academy of Pediatrics has begun developing guidelines on the use of

non-invasive ways to administer oxygen to premature infants starting at birth. In addition, based upon what we have heard from the field and seeing in practice, preliminary trends indicate that physicians treating very premature infants are using higher saturation rates to improve overall outcomes for these fragile infants. Efforts are being made to collect data and verify these trends.

**Has the Neonatal Research Network responded to OHRP's determination on the SUPPORT trial?**

On March 22, 2013, Richard B. Marchase of the University of Alabama responded to OHRP's determination with a plan of corrective action, stating that it had revised the sample consent form provided to its investigators to instruct them "to include the specific risks of all [trial] arms even if those procedures fall within the parameters of the standard of care."

On April 16<sup>th</sup>, the NHLBI/NICHD forwarded copies of all the network's ongoing protocols to Dr. Bohrer in OHRP, including the Transfusion in Prematures (TOP) trial protocol and sample consent form to Dr. Borrer at OHRP.

On May 3, NICHD forwarded copies of all the network's ongoing protocols and sample consent forms to Dr. Borrer at OHRP.

In a June 4 letter to the University of Alabama, OHRP stated that it would suspend its previous decision, stating that it "does not and has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care."

**Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the TOP trial. Will that trial be suspended until new guidance is released?**

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

**TOP Trial Background**

- Anemia is a very common problem in extremely premature infants with 90 percent receiving a transfusion at some point. These infants are less than 1000 grams (2.2 pounds at birth) or even smaller to qualify for the study.
- The infants eligible have a high rate of complications and a death rate of 20-25%.
- Existing studies of when to transfuse this population of infants have produced conflicting and inconclusive results and there is little reliable information upon which to guide practice.

- TOP was undertaken to obtain evidence to give physicians and families a better idea of when an infant should be transfused.

Participation is voluntary.

Per current regulations and procedure, the consent forms are tailored to local institutions and are approved by Institutional Review Boards at the local institutions.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: SUPPORT Trial - UAB response  
**Date:** Thursday, August 29, 2013 11:33:47 AM  
**Attachments:** [3271\\_001.pdf](#)

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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Thursday, April 18, 2013 7:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Clinton Colmenares  
**Subject:** FW: SUPPORT Trial - UAB response

Rose:

Here it is. Let me know if you need anything else.

Wally

---

**From:** Jonathan E Miller [<mailto:jonathanm@uab.edu>]  
**Sent:** Friday, March 22, 2013 4:20 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Richard B Marchase; Laretta Gerrity; Ferdinand Urthaler  
**Subject:** FW: SUPPORT Trial - UAB response

Dr. Carlo,  
Please see attached for UAB's response to OHRP.

Sincerely,  
Jonathan

**Jonathan E. Miller, MPPA, CIP**  
Director, UAB IRB

---

**From:** Jonathan E Miller  
**Sent:** Friday, March 22, 2013 4:12 PM

**To:** Buchanan, Lisa (HHS/OASH)  
**Cc:** Laretta Gerrity; Richard B Marchase; Ferdinand Urthaler  
**Subject:** SUPPORT Trial - UAB response

Ms. Buchanan,

Please find attached UAB's response to OHRP's correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013). Hard copy original documents have been sent to the address noted on the letter.

Please let me know if you have any questions or if I can be of assistance.

Sincerely,  
Jonathan

**Jonathan E. Miller, MPPA, CIP**  
Director, Office of the Institutional Review Board  
University of Alabama at Birmingham  
205-975-3919  
[jonathanm@uab.edu](mailto:jonathanm@uab.edu)



*Office of the Vice President for Research and Economic Development*

March 22, 2013

Lisa R. Buchanan, MAOM  
Compliance Oversight Coordinator  
Division of Compliance Oversight  
Office for Human Research Protections  
The Tower Building  
1101 Wootton Parkway, Suite 200  
Rockville, Maryland 20852

RE: Research Project entitled "The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)  
Principal Investigator: Dr. Waldemar Carlo  
HHS Protocol Number: 2U10HD034216

Dear Ms. Buchanan:

This letter is in response to your correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013) regarding the project referenced above. I am in receipt of a letter from the investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group. Allow me to provide an excerpt from that correspondence:

The investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group would like to first thank OHRP for presenting its concerns clearly and giving us an opportunity to share our thinking about these issues. The Neonatal Research Network investigators are committed to the highest standards of ethical conduct in our human subjects' research, especially where vulnerable participants are concerned. Please ... let us know if we can discuss any of the issues by conference call at your convenience. We welcome the opportunity to engage in a constructive dialogue with OHRP to ensure that if there are opportunities to improve our research practices, we will identify them and incorporate them into our program going forward.

OHRP's letter requested that UAB "provide a plan that the IRB will use to ensure that approved informed consent documents include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a)". The following actions have already been implemented:

- The Office of the Institutional Review Board (OIRB) has revised the sample consent form (see Appendix I) provided to investigators. Information has been added to the Risks and Discomforts section to instruct investigators to include the specific risks of all arms even if those procedures fall within the parameters of standard of care.
- Checklists used by OIRB staff members to ensure both regulatory and institutional requirements are met prior to the IRB approval of a study have been refined to ensure inclusion of all of the basic elements of

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marchase@uab.edu  
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1530 3RD AVE S  
BIRMINGHAM AL 35294-0107

Page 2 of 2

Lisa R. Buchanan – OHRP

March 22, 2013

consent as required by HHS regulations at 45 CFR 46.116(a). The New Protocol Checklist is attached as Appendix II.

- OIRB staff members who coordinate the reviews of research protocols have been reminded that the risks of all study arms must be described in the consent document, even when those arms fall within the parameters of standard of care.

We believe the steps described above will ensure that approved informed consent documents will include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a). The UAB OIRB continually seeks ways to improve its already strong program of human research protection and is appreciative of OHRP's recommendations and guidance.

Please do not hesitate to contact me if OHRP has questions or suggestions in this regard.

Sincerely,



Richard B. Marchase, Ph.D.

Vice President for Research and Economic Development

cc: Ferdinand Urthaler, MD, Chair, UAB IRBs  
Jonathan Miller, Director, UAB Office of the IRB

**Appendix I – UAB IRB Sample Informed Consent Document**

## Sample Consent Form

**It is impossible to address all scenarios for the many types of research protocols conducted by UAB researchers. This sample is designed to assist you in the preparation of consent forms. It is intended to show language preferred by the UAB IRB to address the essential elements of informed consent. In many cases, the sample language will need to be modified, deleted, or expanded for the particular study.**

Shaded paragraphs like this one are instructions for you, the writer. Do not include them in the consent form you submit. If the instructions indicate that specific language applies to your protocol, the specific language will be shown below the instructions outside of the shaded paragraph.

**Use this sample consent form as a guide for obtaining consent and/or assent from participants 14 years of age and older.**

### **Formatting Instructions**

- Use a 12 pt font for the consent form.
- Write the consent form in the 2nd person (i.e., you) and keep the pronoun usage consistent throughout.
- Use *Page X of Y* numbering on each page.
- Leave an area approximately 1 inch by 2 inches on the bottom of the first page for the IRB approval stamp.

### **Use understandable, non-technical language at an 8th-grade or lower reading level.**

- Readability statistics can be displayed in Microsoft Word. Search Microsoft Office Help for "readability statistics" for further instructions.

DELETE THIS FIRST PAGE OF INFORMATION  
IF YOU ARE USING THIS DOCUMENT  
TO CREATE YOUR CONSENT FORM.

## CONSENT FORM

**TITLE OF RESEARCH:** Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

**IRB PROTOCOL:** F#####

**INVESTIGATOR:** John Doe, Ph.D.

**SPONSOR:** If the protocol is being sponsored by UAB departmental funds or is unfunded, put the name of the department here (e.g., UAB Department of Medicine). For student research, include the student's departmental affiliation.

If additional or other support is being provided, include this information with a heading such as "**SUPPORTED BY:**" After the SPONSOR line.

**SPONSOR:** Wise Drug Company, Inc.

### RESEARCH INVOLVING CHILDREN:

- When a parent or guardian is providing consent for only the child participant who will sign the assent section of the consent form, do not use "you/your child" throughout the form. Instead, use "you" and insert the following text after the SPONSOR line and before the Purpose of the Research section:

*For Children (persons under 19 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").*

- When a parent or guardian is providing consent for only the child participant who will sign a separate assent form or who will not provide written assent, use "your child" throughout the form.
- When a parent or guardian is providing consent for both him/herself and the child participant, specify throughout the consent form when you are referring to the parent and when you are referring to the child. This would allow for the use of "you," "your child," and "you and your child" throughout the form.

### Purpose of the Research

- Explain the purpose of the study in nontechnical language.
- Describe why the participant is being asked to join.
- State that the study involves research.
- If drugs or devices are used, indicate whether they are FDA approved or investigational.
- If applicable, explain what a Pilot, Phase I, II, III, or IV drug study is.
- State the total planned number of participants (e.g., individuals, records, specimens) to be enrolled by the UAB investigator, and studywide for multicenter studies.

We are asking you to take part in a research study. This research study will test how well a new drug lowers blood pressure. The new drug, Trimycin, is investigational and not yet approved by the U.S. Food and Drug Administration (FDA). People who enter into the study will take either the new drug, Trimycin, or Hydrochlorothiazide (water pill). Hydrochlorothiazide is the FDA approved drug that most people take now to lower blood pressure. Trimycin is approved in Europe, but has not been approved in the United States. More than 200 people in other research studies in the United States have safely used Trimycin. This is a Phase III study. A Phase III study is a research study that looks at a large number of patients receiving a common or routine treatment. This study will enroll 200 participants nationwide, and 20 of them will come from UAB.

### **Explanation of Procedures**

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- Describe the procedures to be followed, identifying which procedures are for research and which procedures are standard of care.
- Identify which procedures are experimental.
- Estimate the amount of time involved in study participation.
- If specimens (e.g., blood, tissue, body fluids) will be collected as part of the research procedures, describe the collection in this section. If the specimens will be stored for future research, describe the storage procedures under "Storage of Specimens for Future Use."

If you enter the study, all your current blood pressure medicines will be stopped for 1 month. During this time, you will be given pills called placebos. A placebo does not have any active medicine, so it should not have any effect on your blood pressure. However, this placebo might cause your blood pressure to lower. The study staff will need to watch your blood pressure closely while you are not on any medicine for your blood pressure. Your blood pressure will be watched to make sure it does not rise so high that you need immediate treatment. You will need to come for office visits three times during the first week. You will need to come for office visits two times per week during Weeks 2, 3, and 4. If your blood pressure is in the range required after Week 4, you will be entered into the study. If your blood pressure is not in the range required after Week 4, you will not be entered into the study and will receive standard care for your blood pressure. If you are entered and complete the entire study, you will be in the study for 6 months. If you qualify for the study, you will be randomly picked (like the flip of a coin) by a computer to receive either Trimycin or Hydrochlorothiazide. You will take the medicine once a day by mouth. This will be a double-blind study. This means neither you nor your doctors will know which medicine you are taking. If medically necessary, the doctor can find out which drug you are taking.

These tests will be made during the study: lab blood tests, urine tests, weight measures, resting electrocardiogram, heart rate, and blood pressure. (An electrocardiogram measures the electrical activity of the heart.) You will be asked to come back to the clinic for 20 weekly visits. At each visit you will be asked if you have had any bad reactions and how you are feeling on the drug.

If drug screening is part of the protocol, include a statement such as:

If you have used any illicit (street) drug(s) within the past 3 months, we ask that you not participate in this project.

Where HIV testing is conducted, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling before and after the testing.

Where other protocol testing for reportable diseases is conducted, individuals will be informed of the results and told where to obtain counseling and referred to their primary care physician or the state health department.

### **Incidental Findings**

---

If research-only imaging studies are part of the protocol, address whether or not the images will be read for incidental findings. If the images will not be read for incidental findings, include the following:

We are performing imaging solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. Under no circumstance will the investigator, research staff, or imaging staff interpret the scan as normal or abnormal. They are unable to make any medical comments about your scan. The scan will not be looked at or read for any healthcare treatment or diagnostic purpose. If you want your scan to be reviewed by a physician so that the physician can look for medical issues, you can request a copy of your scan. We will provide an electronic copy at no charge.

### **Risks and Discomforts**

---

- Include any foreseeable risks or discomforts to the participant (e.g., physical, social, financial, loss of employability, reputation, and breach of confidentiality).
- When possible, quantify the risks involved (e.g., *common, rare, percentages*).
- If the study involves a placebo,
  - define placebo (not as *treatment or medication*; see paragraph above that begins "*If you enter the study...*")
  - describe what complications may result
  - describe the precautions that will be taken to protect the participant during this time.
- Do not include risks or discomforts associated with drugs or interventions that are not being administered or performed as part of this study.

You may have some side effects from taking these drugs. The side effects of Trimycin are headaches, feeling drowsy, and feeling tired. About forty percent (40%) of people who take Trimycin have reported feeling drowsy and tired. About twenty percent (20%) of people who take Trimycin have headaches. Hydrochlorothiazide can cause the following side effects: low blood potassium; a rise in blood uric acid and blood sugar; and a lowering of red and white blood cells. About eighty percent (80%) of people who take Hydrochlorothiazide have these problems. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

**Randomization:** If your protocol involves randomization, include a paragraph on risks of randomization. Ensure the risks of all study arms are described in detail in this section, even if the procedures in those arms would be standard of care if the participant was not in the study. For example:

You will be assigned to a treatment group by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

### **Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child**

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If applicable, include this section and address the precautions that should be taken by women of childbearing potential and/or by men capable of fathering a child before, during, and/or after participation. List the specific acceptable methods of birth control for participants involved in the study. Use only the information that is applicable to the study population.

We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Women who can become pregnant must take a pregnancy test before the start of the study.

You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex.

Unless you cannot have children because of surgery or other medical reasons, you must have been using an effective form of birth control before you start the study. You must also agree to continue to use an effective form of birth control for 6 months after taking the study drug. Effective birth control includes birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant.

### **Benefits**

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- State any potential benefits to the participant or to others that may reasonably be expected from the research.
- Do not overstate benefits.
- If there is no potential for direct benefit to the participant, that should also be stated.
- **Do not include** medication, treatment, devices, or compensation information.

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat high blood pressure in the future.

### **Alternatives**

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- Include appropriate alternative procedures or courses of treatment that may be advantageous to the participant.

- One alternative may be to not participate in the study.

There are many other drugs that are used to treat high blood pressure. Some examples of these drugs are Betasan, Enapror, and Ditserin. The investigator or research staff will discuss these other drugs with you.

### **Confidentiality**

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- Include information regarding anyone who will receive identifiable data (e.g., through subcontracts or other agreements).
- Include the US Food and Drug Administration (FDA) if the research involves a drug, device, or biologic subject to FDA oversight.

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of [ADD SPONSOR NAME] and the Office for Human Research Protections (OHRP). The results of the treatment may be published for scientific purposes. These results could include your [ONLY INCLUDE APPLICABLE] lab tests and X-rays. However, your identity will not be given out.

**Permanent Medical Record:** If the consent form will be placed in the participant's permanent medical record at University of Alabama Hospital and/or The Children's Hospital of Alabama, include the following:

If any part of this study takes place at

[UAB ONLY] University of Alabama Hospital  
[TCHA ONLY] The Children's Hospital of Alabama  
[UAB & TCHA] University of Alabama Hospital and The Children's Hospital of Alabama

this consent document will be placed in your file at that facility. The document will become part of your medical record chart.

**Billing Compliance Language:** Only if "clinical billable services" will be provided at a UAB Health System location (i.e. HSF Clinics, UAB Hospital, UAB Highlands, or Callahan Eye Foundation) or The Children's Hospital of Alabama, include the language below, as applicable. If you have questions about UAB's clinical trial billing, contact the Fiscal Approval Process (FAP) staff at [FAP@uab.edu](mailto:FAP@uab.edu). For details on submission requirements, go to <http://www.uab.edu/osp/fiscal-approval-process-fap>. If you have questions about clinical trial billing for studies conducted at The Children's Hospital of Alabama, contact Pam Barlow at [pam.barlow@chsys.org](mailto:pam.barlow@chsys.org) or 558-2452.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of

[UAB ONLY] UAB and UAB Health System affiliated entities  
[TCHA ONLY] The Children's Hospital of Alabama and its billing agents

[UAB & TCHA] UAB and UAB Health System affiliated entities, along with The Children's Hospital of Alabama and its billing agents

so that claims may be appropriately submitted to the study sponsor or to your insurance company for clinical services and procedures provided to you during the course of this study.

**International Protocols:** Only if the study is conducted outside the United States or sponsored by a company based outside the United States and foreign regulatory agencies will have access to identifiable research records, include the following:

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

**ClinicalTrials.gov:** For applicable clinical trials, include the statement below. It is the responsibility of the sponsors and investigators to determine if their clinical trial meets the definition of an "applicable clinical trial" and to ensure compliance with the most current applicable statutory and regulatory requirements. If you have any questions regarding registering a study on ClinicalTrials.gov, contact Penny Jester at 934-2424 or [pjester@uab.edu](mailto:pjester@uab.edu).

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**Reportable Diseases/Conditions:** Only if the investigator will be testing for any reportable diseases/conditions, include a statement specifying what reportable diseases/conditions are being tested and that positive results will be reported to the county or state health department.

**Screening for Drugs, Observations of Abusive Behavior:** Only if the investigator will conduct drug screening or inquire about abusive behavior (e.g., child or elder abuse or neglect, or harm to self) as part of the protocol, include the following statement:

Information obtained during the course of the study which, in the opinion of the investigator(s), suggests that you may be at significant risk of harm to yourself or others will be reportable to a third party in the interest of protecting the rights and welfare of those at potential risk.

**Genetic Research:** Only if the research involves genetic testing, describe the protections provided to the participant under GINA. For questions regarding GINA, see the IRB Guidebook. The following may be used for the description:

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

### **Voluntary Participation and Withdrawal**

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- Include the consequences of a participant's decision to withdraw from the research.
- Include procedures for orderly termination of participation by the participant.
- If applicable, include anticipated circumstances under which the PI without regard to the participant's consent may terminate the participant's participation (see second paragraph below).

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

**If students or employees of UAB may participate in the study, the IRB recommends using the following language in the consent form:**

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

### **Cost of Participation**

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- If any costs to the participant or the participant's health insurance might result from the research (e.g., for tests, drugs, biologics, devices, or copayments), describe those costs. Include information about any financial assistance that may be available, such as how to consult a social worker.
- If there is no cost to the participant, this should be stated.

There will be no cost to you for taking part in this study. All drugs, exams, and medical care related to this study will be provided to you at no cost during the 6-month study period.

**If standard medical care may be provided during the study include the following statement:**

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

**If participants may be enrolled in Medicare Advantage and will have study related services billed to their Medicare Advantage insurance, include the following statement. If you have questions regarding the inclusion of this statement, contact the Fiscal Approval Process (FAP) staff at [FAP@uab.edu](mailto:FAP@uab.edu).**

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

### **Payment for Participation in Research**

- Note: Payment may not be based upon successful completion of the protocol.
- Specify the amount and type/method of compensation a participant will receive for participating OR that there is no compensation for participation.
- If applicable, include the payment schedule.
- Describe prorated payments for participants who withdraw before the end of the study.
- If children are involved, specify whether the child or parent is being paid.

You will be paid \$10 for each study visit, including the placebo phase of the study. If you quit the study, you will be paid \$10 for each study visit made to the clinic. Payments will be made after 3 months and 6 months if you complete the entire study. Payments will be made by check sent to you in the mail. If you do not finish the entire study, you will be paid at the time you decide to stop taking part in the study. If you complete the entire study, you will receive a total of \$290.

**If a participant is to earn \$600 or more in a calendar year from their participation in research, include the following language:**

You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive. You will receive a form 1099 in January of the year following your participation in this study. This form is also sent to the IRS to report any money paid to you. No taxes are kept from your check.

### **Payment for Research-Related Injuries**

- Include this section only if the research involves (a) greater than minimal risk or (b) procedures or interventions that could result in harm or injury.
- If the section is to be included, include the UAB statement below.

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

In addition, if the research is sponsored, include language that addresses whether or not the sponsor(s) will provide compensation for research-related injuries.

- For sponsored research where the sponsor(s) **will not** pay for compensation to injured research participants or pay for medical treatment of research-related injuries, list the names of all sponsors after "UAB".

UAB and Wise Drug Company, Inc. have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

- For sponsored research where the sponsor(s) **will** pay participants for either compensation or treatment for research-related injuries, include the specific language provided by the sponsor(s) regarding injury compensation. The IRB must be provided with "sponsor verification" either in the form of a letter signed by the sponsor(s) with the same wording given in the consent form or a model consent form included in the protocol and listed in the Table of Contents of the protocol with the same wording. Do not submit a copy of the indemnification letter as the verification. Include information regarding what medical treatment will consist of if injury occurs and where further information may be obtained.

### **Significant New Findings**

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Indicate that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant by the principal investigator or his/her staff.

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

### **Genome-Wide Association Studies (GWAS)**

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For protocols that are considered Genome-Wide Association Studies (GWAS), UAB must certify that plans for the submission of genotype and phenotype data from GWAS to the NIH meet the expectations of the policy. See the IRB Guidebook for more information on what should be submitted for this certification. For applicable protocol, include the following:

The DNA that composes your genes will be analyzed and that data, which is referred to as your genotype or complete genetic makeup, will be compared to your phenotype, which consists of your observable traits, characteristics, and diseases. Your genotype and phenotype data will be shared for research purposes through the National Institutes of Health (NIH) Genome-Wide Association Studies (GWAS) data repository. The aim of this research is to discover genetic factors that contribute to the development, progression, or therapy for a particular disease or trait.

## **Questions**

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- Include the name of the Principal Investigator and his/her contact number for participants to contact regarding the research and research-related injuries.
- Include the names of additional contact personnel, if applicable.

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, you may contact Dr. John Doe. He will be glad to answer any of your questions. Dr. Doe's number is 205-934-3810. Dr. Doe may also be reached after hours by paging him at 205-934-3411 (beeper 9999).

Include for the Office of the IRB contact information.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

## **Legal Rights**

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You are not waiving any of your legal rights by signing this informed consent document.

## **Storage of Specimens for Future Use**

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If specimens (e.g., blood, tissue) obtained for the research may be stored for research not specifically defined in the protocol, place this section after Legal Rights and before Signatures. At a minimum, address the following points and include lines for participants to initial (do not use checkboxes):

- What kind of specimens will be collected and the means of collection.
- What type of research will be done with the specimens.
- Whether the specimens will be shared with other investigators
- Whether the specimens will be coded or anonymized (no way of tracing back to participant/uncoded or code destroyed).
- Whether the participant may be contacted for additional consent.
- How long, if known, the biological specimens will be stored. (Short-term: current protocol only or other current research; Long-term: future studies on disease or condition, repository, etc.).
- Foreseeable risks or benefits to participants in the collection, storage, and subsequent research use of specimens.
- What will be done with the biological specimens if the participant refuses permission.
- What will be done with the research results. (Research results should not be placed in the individual participant's medical record.)
- Potential for commercial use of the subject's specimen(s).
- How to withdraw consent for future use.

As part of this study, we would like to store some of the blood and urine specimens collected from you for future research on hypertension. The future research may be conducted by Dr. John Doe or by other researchers that obtain IRB approval for their research. The specimens will be

labeled with a code that only Dr. John Doe can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur.

You do not have to agree to allow your blood and urine specimens to be stored in order to be part of this study.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Dr. John Doe at the University of Alabama at Birmingham at 205-934-3810. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial your choice below:

I agree to allow my samples to be kept and used for future research on hypertension.

I do not agree to allow my samples to be kept and used for future research.

### Signatures

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**It is impossible to address all scenarios for signature requirements that may be needed for various types of research. These instructions and samples are designed to assist you in the preparation of the Signatures section. In many cases, the Signatures section will need to be customized for the particular study population.**

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol.
- Each signature-date line included in the Signatures section, as applicable to the research, must be signed and dated.
- All signatures must appear on the same page, but that page does not need to be a separate page with no other information.
- Each person who signs the consent form must include the date of his/her signature.
- If the research involves children (i.e., individuals younger than 19 years of age for research conducted in the state of Alabama), see "Children" under General Information in the IRB Guidebook and see Example Signatures for Research Involving Children, below.
- If the research involves pregnant women, see "Pregnant Women, Fetuses, Neonates" under General Information in the IRB Guidebook.
- A signature-date line for the participant must be included. The three acceptable options are shown and described below.

Your signature below indicates you agree to participate in this study. You will receive a copy of this signed consent form.

**Option 1**

---

Signature of Participant

Date

**Option 2**

---

Signature of Participant or Legally Authorized Representative

Date

**Option 3**

---

Signature of Participant

Date

---

Signature of Legally Authorized Representative

Date

**Legally Authorized Representatives (LAR)**

- If the research proposes to obtain consent from the participant **or** the LAR, add "(or Legally Authorized Representative)" after "Signature of Participant."
- If the research proposes to obtain consent from the participant **and** the LAR, include a separate signature-date line for each person.
- If an individual is not capable of providing informed consent, the IRB allows that it may be obtained from the individuals listed below in priority order:
  - Judicially appointed guardian or individual named in a durable power of attorney;
  - Spouse;
  - Sons or daughters 19 years of age or older;
  - Either parent;
  - Brother or Sister 19 years of age or older;
  - Other nearest kin 19 years of age or older.

---

Signature of Principal Investigator

Date

- All persons who discuss or obtain informed consent must be listed in the HSP.
- If the principal investigator is not the only person who will conduct informed consent discussions and obtain signatures, add "or Other Person Obtaining Consent" after "Signature of Principal Investigator."
- If the Principal Investigator will never obtain informed consent, this signature-date line should be labeled "Signature of Person Obtaining Informed Consent."

---

Signature of Witness

Date

- Include this line unless the PI requests and justifies, and the IRB approves a waiver of the witness requirement.
- The person administering the consent (e.g., study coordinator) cannot sign as the witness.

Reviewed by:

---

Signature of Principal Investigator Reviewing Consent Document

Date

Include this line **only if** the HSP specifies that the principal investigator will not obtain informed consent but will only review signed consent documents.

### **Signatures for Research Involving Children**

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate.

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol. See the instructions and options below.
- The UAB IRB usually recommends the following:
  - Waiver of assent needs to be documented for participants under 7 years of age, but these participants should be included in the consent process if possible.
  - A separate assent form should be prepared for use with, and to document the assent of, participants who are 7-13 years old.
  - Participants 14-18 years old document their assent by signing the main consent form.
- If the IRB determines the permission of only one parent or guardian is necessary, only include one line for "Signature of Parent or Guardian" below.
- A parent, for purposes of consent, means either a child's biological or adoptive parent. In some instances, the consent of a guardian may be used in lieu of parental consent. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. For purposes of research conducted in Alabama a *guardian* is:
  1. A person appointed guardian of a child pursuant to the Alabama Uniform Guardianship and Protective Proceedings Act (Code of Alabama, Title 26) as documented by a valid court order;
  2. A person having legal custody of a child and as documented by court order;
  3. A person acting *in loco parentis*, regardless of whether such is documented by a court order. A person acts *in loco parentis* of a child where the individual voluntarily assumes responsibility for the child's custody, care, and maintenance even though no court order exists formally appointing the person as the guardian, legal custodian, or adoptive parent of the child. If such individuals may provide permission for the enrollment of children, the Human Subjects Protocol must explain how the investigator will confirm the *in loco parentis* relationship.

You will receive a copy of this signed informed consent document.

Signature of Participant 14-18 Years of Age	Date
Signature of Parent or Guardian	Date
Signature of Parent or Guardian	Date
Signature of Investigator or Person Obtaining Consent	Date

---

Signature of Witness

Date

If the assent of any child participant may be waived, include the following section with the applicable reason(s) for waiver of assent marked:

**Waiver of Assent**

---

The assent of \_\_\_\_\_ (name of child/minor) was waived because of:

Age \_\_\_\_\_ Maturity \_\_\_\_\_ Psychological state of the child \_\_\_\_\_

---

Signature of Parent or Guardian

Date

---

Signature of Parent or Guardian

Date

---

Signature of Investigator or Person Obtaining Consent

Date

---

Signature of Witness

Date

**University of Alabama at Birmingham**  
**AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION**  
**FOR RESEARCH**

---

**What is the purpose of this form?** You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

**Participant Name:** \_\_\_\_\_  
**Research Protocol:** Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

**UAB IRB Protocol Number:** F#####  
**Principal Investigator:** John Doe, Ph.D.  
**Sponsor:** Wise Drug Company, Inc.

**What health information do the researchers want to use?** All medical information and personal identifiers, including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

**Why do the researchers want my health information?** The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

**Who will disclose, use and/or receive my health information?** The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

**How will my health information be protected once it is given to others?** Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

**How long will this Authorization last?** Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

**Can I cancel the Authorization?** You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

**Can I see my health information?** You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: \_\_\_\_\_

Date: \_\_\_\_\_

or participant's legally authorized representative: \_\_\_\_\_

Date: \_\_\_\_\_

Printed Name of participant's representative: \_\_\_\_\_

Relationship to the participant: \_\_\_\_\_

## **Appendix II – New Protocol Checklist**

### New Protocol Checklist

Full Convened       Research no more than minimal risk (Expedited Category # \_\_\_\_\_)  
 Principal Investigator: \_\_\_\_\_ FAX: \_\_\_\_\_ IRB Protocol #: \_\_\_\_\_

Contact Person: \_\_\_\_\_ PHONE: \_\_\_\_\_  IRAP Created

Protocol Title: \_\_\_\_\_

Faculty Sponsor: \_\_\_\_\_ Training Complete: Y N - Needed for: \_\_\_\_\_

Sponsor: \_\_\_\_\_  DOD  DOE  DE  DOJ/NIJ/Bureau of Prisons  ICH/GCP applies

OSP Proposal # \_\_\_\_\_  Funding App/Grant  Subcontract  MTA  CDA  DUA  FFS

<input type="checkbox"/> HSP	<input type="checkbox"/> Sponsor Protocol (date) _____	
<input type="checkbox"/> PORF or CTRC	<input type="checkbox"/> Titles Match - <input type="checkbox"/> Grant/Sponsor Protocol <input type="checkbox"/> HSP <input type="checkbox"/> ICF	
<input type="checkbox"/> 1572	<input type="checkbox"/> IB, Package Insert, or Device Manual _____	
<input type="checkbox"/> Waiver of IC	<input type="checkbox"/> Waiver of Auth & IC	<input type="checkbox"/> Waiver of IC Documentation
<input type="checkbox"/> Consent/Assent Form(s) # _____	<input type="checkbox"/> Sponsor Sample CF	<input type="checkbox"/> ICH/GCP criteria met (if applicable)
<input type="checkbox"/> Title, IRB Protocol #, Investigator, & Sponsor/Support	<input type="checkbox"/> Alternatives	<input type="checkbox"/> Payment for Participation
<input type="checkbox"/> Version Date	<input type="checkbox"/> Confidentiality	<input type="checkbox"/> UAB Injury Statement
<input type="checkbox"/> Page #s	<input type="checkbox"/> Permanent Medical Record	<input type="checkbox"/> Sponsor Injury Statement
<input type="checkbox"/> You/your child box	<input type="checkbox"/> UAB <input type="checkbox"/> TCHA	<input type="checkbox"/> Sponsor Verification
<input type="checkbox"/> Purposes of the Research	<input type="checkbox"/> Billing Compliance	<input type="checkbox"/> New Findings
<input type="checkbox"/> Statement re: research	<input type="checkbox"/> UAB <input type="checkbox"/> TCHA	<input type="checkbox"/> GWAS
<input type="checkbox"/> Explanation of Procedures	<input type="checkbox"/> International Protocol	<input type="checkbox"/> Name/Number (Research/Injury)
<input type="checkbox"/> Identify experimental procedures	<input type="checkbox"/> Clinical Trials.gov	<input type="checkbox"/> Name/Number (Participant Rights)
<input type="checkbox"/> Expected duration of participation	<input type="checkbox"/> Reportable Diseases/Conditions	<input type="checkbox"/> Legal Rights
<input type="checkbox"/> Incidental Findings	<input type="checkbox"/> Screen Drugs/Observe Abuse Behavior	<input type="checkbox"/> Storage of Specimens
<input type="checkbox"/> Risks and Discomforts	<input type="checkbox"/> Genetic Research/GINA	<input type="checkbox"/> Signatures
<input type="checkbox"/> Randomization risks	<input type="checkbox"/> Voluntary Participation & Withdrawal	<input type="checkbox"/> Assent of Child/Waiver of Assent
<input type="checkbox"/> Childbearing &/or Fathering	<input type="checkbox"/> Student/Employees	<input type="checkbox"/> HIPAA
<input type="checkbox"/> Benefits	<input type="checkbox"/> Cost of Participation	
	<input type="checkbox"/> Cost of SMC	<input type="checkbox"/> FAP
	<input type="checkbox"/> Medicare Advantage language	

<input type="checkbox"/> Pharmacy Release	<input type="checkbox"/> TKC, notif attached - Y N
<input type="checkbox"/> Radiation Safety Approval	<input type="checkbox"/> UH, notif attached - Y N
<input type="checkbox"/> Infection Control Approval	<input type="checkbox"/> UAB Highlands, notif attached - Y N
<input type="checkbox"/> Pathology Release	<input type="checkbox"/> TCHA, notif attached - Y N
<input type="checkbox"/> IBC Approval	<input type="checkbox"/> EFH, notif attached - Y N
<input type="checkbox"/> CIRB Conflict Identified	<input type="checkbox"/> CRU, notification attached - Y N
<input type="checkbox"/> Include CIRB Language	<input type="checkbox"/> Other UAB sites _____
<input type="checkbox"/> FERPA Applies	<input type="checkbox"/> Non UAB sites _____
<input type="checkbox"/> PPRA Applies	Engaged in Research: Y N      If yes, IRB approvals Y N

<input type="checkbox"/> Children - CRL# _____	<input type="checkbox"/> Pregnant Women & Fetuses	<input type="checkbox"/> Nonviable or UV Neonates	<input type="checkbox"/> Decisionally Impaired
<input type="checkbox"/> Prisoners - Cat# _____	<input type="checkbox"/> Student/Employees	<input type="checkbox"/> Non-English Speakers	
<input type="checkbox"/> Recruitment Materials _____		<input type="checkbox"/> Partial Waiver of Authorization	
<input type="checkbox"/> SAE Log submitted. Date/numbers _____		<input type="checkbox"/> Screening Script/Questionnaire	
<input type="checkbox"/> Other Questionnaires _____			

Phase: \_\_\_\_\_  DSMB  Int. Analysis  Sponsor/PI Monitoring Plan  Plan Described  
 Describes alternate plan for SAE reporting  Board approved at meeting?  
 Requests waiver of 24 hour "think it over"  Board approved at meeting?

Drugs/Devices Name and IND/IDE Number \_\_\_\_\_

IRB pre-start up visit taken place, if Investigator is both sponsor and holder of IND/IDE  IRAP Approved

**WRITE REVIEWER NOTES ON BACK OF THIS PAGE.**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A  
**Date:** Thursday, August 29, 2013 11:10:12 AM  
**Attachments:** [RE request for protocols and informed consent documents.msg](#)  
[FW request for protocols and informed consent documents.msg](#)

---

Here are the emails documenting the correspondence sent to OHRP regarding our other studies – we have confirmed receipt from OHRP and have had no additional correspondence.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 10:59 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: Updated support Q and A

Working on it now. Please see below.

Rose, have we responded in an official capacity for the NRN? Or is it just UofA's response?

I've got your TOP talking points.

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 10:50 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: Updated support Q and A

Can we add stuff about 1) How the (b)(5) actions and 2) (b)(5) specifically?

Alan E. Guttmacher, M.D.  
Director  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

National Institutes of Health  
31 Center Drive  
Building 31, Room 2A03  
Bethesda, MD 20892-2425

Phone: 301-496-3454  
e-mail: [gutmach@mail.nih.gov](mailto:gutmach@mail.nih.gov)  
url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 10:42 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Updated support Q and A

Please see attached, fyi.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** FW: OR and CI for comparing SUPPORT and non-enrolled groups  
**Date:** Thursday, August 29, 2013 9:51:53 AM  
**Importance:** High

---

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, April 25, 2013 11:47 AM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: OR and CI for comparing SUPPORT and non-enrolled groups  
**Importance:** High

Here is the information for the enrolled vs. non-enrolled. The point estimate is below – favors

(b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, April 25, 2013 11:39 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Das, Abhik  
**Subject:** OR and CI for comparing SUPPORT and non-enrolled groups

Rose,

Abhik asked me to send you the adjusted odds ratio and 95% confidence interval for comparing mortality between infants enrolled in SUPPORT and those eligible but not enrolled. In the model created for the second antenatal consent paper, which adjusted for center, GA, birth weight, gender, race, and antenatal steroids, the OR (95% CI) for death for enrolled vs. non-enrolled infants was 0.88 (0.73, 1.06). The p value was 0.16. Although not statistically significant, the point estimate favored infants who were enrolled in SUPPORT. Let me know if you need any additional information.

Marie

**Marie Cantz, Ph.D.**  
**Senior Research Statistician**  
**RVI International**  
**[mcantz@rvi.org](mailto:mcantz@rvi.org)**  
**919-537-5110**

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Subject:** Final Support Internal QA April 18 3  
**Date:** Thursday, August 29, 2013 9:43:57 AM  
**Attachments:** [Final Support Internal QA April 18 3.docx](#)

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### **What is the SUPPORT Study?**

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) study was a large clinical trial that sought to determine how best to deliver oxygen to very small preterm infants and determine the ideal oxygen saturation targets for these very fragile newborns. The study compared the traditional means of providing oxygen, ventilator therapy with surfactant, to continuous positive airway pressure (CPAP), in which air is blown through a preterm infant's nostrils to gently inflate the lungs. When the study began, the standard treatment was to maintain oxygen levels in the range of 85 to 95 percent. The researchers sought to identify within this standard range the percentage of oxygen saturation that would minimize the risk of retinopathy of prematurity. Previous studies had shown that prolonged exposure to high levels of oxygen could increase the risk of retinopathy of prematurity, a complication of oxygen therapy that affects the retina and can sometimes result in vision loss. The study was divided into two arms, each of which proceeded at the same time, in the same group of infants. In the first arm, each infant had a 50 percent chance of receiving higher oxygen target saturation levels, and a 50 percent chance of receiving lower levels. In the second arm, each infant had a 50 percent chance of receiving oxygen by CPAP and a 50 percent chance of being assigned to the ventilator group.

### **What did the SUPPORT Study find?**

The researchers found that the higher range increased the chances of survival but also increased the chances for ROP. This unexpected but critical finding informed clinical practice. The researchers also concluded that CPAP therapy was as effective as ventilator therapy, and resulted in fewer complications.

### **How did mortality rates from the study compare to those of infants not in the study?**

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

#### ***Percent Mortality (Unadjusted data):***

Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

### **Had the researchers anticipated a lower survival rate for the infants in the lower oxygen range?**

No. The finding of a lower survival rate for those at the lower range was not anticipated or expected. At the time of the study, clinical practice for providing oxygen to very preterm babies varied widely. A target range of 85-95 percent was generally standard clinical practice and in 2007 was recommended by the American Academy of Pediatrics. In fact, at the time, emerging research showed that providing oxygen at the lower end of the acceptable range reduced the

risk of retinopathy without increasing the risk of death and neurodevelopmental impairment. As a result, physicians were starting to use the lower oxygen range to treat very preterm babies.

**Has the Office for Human Research Protections (OHRP) criticized the design or rationale for the study?**

It is critical to note that the treatments or the rationale of the study has never been in question by the Office for Human Research Protections.

**What had OHRP objected to?**

The OHRP cited the study for not including language, specifically in the risk/benefit section of the consent form, about research conducted in the 1950s suggesting the risk of death was higher with oxygen restriction.

**Why had the researchers not included this language?**

The older ROP studies were conducted before the widespread use of ventilators, pulse oximetry, and other sophisticated oxygen monitoring and measurement devices. The risk/benefit description under the oxygen saturation section of the consent form included language that reflected the available information/knowledge/data the oxygen administered at the lower saturation range reduced the risk of retinopathy. Since the current research had not shown a higher risk of death and neurodevelopmental impairment at any of these saturation levels (85-95%), the study authors did not list death and neurodevelopmental impairment as potential risks.

**Were parents adequately informed of the study risks?**

In addition to the consent form, representatives of the study explained the purpose of the research and its potential risks and benefits to parents and responded to their questions and concerns.

**Has the OHRP expressed any additional concerns with the study?**

In an interview with the New York Times (but not in the original letter to the Principal Investigator's institution, the University of Alabama), the Director of OHRP, Jerry Menikoff said: "Based on their very hypothesis, they were thinking that there might well be a difference...Being in the higher end [of the oxygen saturation range] should have put you at greater risk of developing eye disease." The parents were informed in the consent form that their children would be assigned at random to the higher or lower range. They were also told that they believed children at the lower range would be less likely to develop ROP. However, it was not explicitly stated that children at the higher range might be more likely to develop ROP.

OHRP has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care.

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There is currently a difference in scientific view between OHRP and NIH (NEJM Hudson, Guttmacher, Collins) with respect to the reasonable foreseeable risks at the time the study was begun.

**In addition to the consent form, were there any other safeguards to ensure that the infants would receive the optimal care?**

Attending physicians were allowed to override the settings if they thought their patients were in danger, and provide either more or less oxygen if they thought that following either course was in their patients' best interest. In addition, attending physicians and parents were free to ask that their children be withdrawn from the study at any time.

**What is the purpose of the Neonatal Research Network (NRN)?**

The NRN, which is currently composed of 18 medical research institutions, was established in 1986 to conduct clinical trials and observational studies in neonatal medicine to help reduce infant morbidity and mortality, and promote healthy outcomes.

Consistent with this mission, between 2000 and 2009, deaths of preterm infants declined 5.5%, from 109.75 per 1,000 live births to 103.48. Death rates for "early" preterm infants, those born before 32 weeks, declined 4.9% from 180.95 to 172.15 per 1,000 live births. In addition, NRN findings have helped to change clinical practice and improve outcomes for premature infants, such as:

- ✓ Identifying a safe way to protect newborns whose brains were getting insufficient oxygen
- ✓ Showing that providing additional Vitamin A to infants under 1,000 grams significantly reduced their risk of death or getting chronic lung disease
- ✓ Showing that giving intravenous immune globulin to reduce hospital-acquired infections in very low birthweight infants, actually increased rates of an often fatal intestinal condition in newborns
- ✓ Showing that giving additional glutamine, an amino acid, to extremely low birthweight infants did not reduce their risk of death or sepsis

**What are the implications of the SUPPORT study findings?**

The SUPPORT findings have already begun to change clinical practice. Based on the study findings, the American Academy of Pediatrics has begun developing guidelines on the use of on invasive ways to administer oxygen to premature infants starting at birth. In addition, preliminary trends indicate that physicians treating very premature infants are using higher saturation rates to improve overall outcomes for these fragile infants.

**What are the implications of the SUPPORT study findings?**

The SUPPORT findings have already begun to change clinical practice. Based on the study findings, the American Academy of Pediatrics has begun developing guidelines on the use of

non-invasive ways to administer oxygen to premature infants starting at birth. In addition, based upon what we have heard from the field and seeing in practice, preliminary trends indicate that physicians treating very premature infants are using higher saturation rates to improve overall outcomes for these fragile infants. Efforts are being made to collect data and verify these trends.

## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Thursday, August 29, 2013 9:17 AM  
**To:** Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wood, Gretchen (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Alexander, Rashada (NIH/OD) [E]; Tatem, Anne (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]  
**Subject:** FW: AP: Preemie study sparks debate: How much should patients know about risks of research

FYI

### **John Burklow**

Associate Director for Communications and Public Liaison  
National Institutes of Health  
Building 1, Room 344  
(301) 496-4461 (phone)  
(301) 496-0017 (fax)  
[burklowj@od.nih.gov](mailto:burklowj@od.nih.gov)



**Celebration of Science at NIH:** *watch how medical research saves lives and improves health*

---

**From:** Sye, Tait (OS/ASPA)  
**Sent:** Thursday, August 29, 2013 8:59 AM  
**To:** Broido, Tara (HHS/OASH); Lewis, Caya (HHS/IOS); Lee, Noelle C. (HHS/IOS); Gianelli, Diane M (OASH); Burklow, John (NIH/OD) [E]; Salcido, Dori (HHS/ASPA); Myles, Renate (NIH/OD) [E]; Bradley, Ann (HHS/OASH); Horowitz, David (HHS/OGC); Baldauf, Sarah (OS/ASPA)  
**Subject:** AP: Preemie study sparks debate: How much should patients know about risks of research

Here is AP story on the public meeting. Didn't make it into the clips. Will include it in tomorrow's. No mention of the press conference.

Actually does a very good job of explaining the issues.

\*\*\*  
AP: Preemie study sparks debate: How much should patients know about risks of research

By LAURAN NEERGAARD AP Medical Writer  
August 29, 2013 - 3:23 am EDT

<http://www.therepublic.com/view/story/f5d99a77e7064ef7b6c88e74e0b4fd7f/US-MED--HealthBeat-Research-Risks>

WASHINGTON — Dagen Pratt's parents enrolled their tiny premature baby in a study of oxygen treatment believing she'd get the best possible care. They didn't understand it was an experiment to test what dose

works best. No one mentioned any risks.

Now 6, Dagen struggles with cerebral palsy, and they wonder: Is that long-ago study to blame?

"Tell me that the Support study did not hurt Dagen in any way," her father, Shawn Pratt, challenged a government panel on Wednesday as his daughter, dressed in a bright sundress, stood quietly by.

A major controversy has erupted over what sounds like a straightforward question: How much should patients be told about the potential risks before they're enrolled in certain kinds of medical research?

The issue isn't about how to study a brand-new, unapproved therapy. All sides agree that those studies must fully inform participants that there's no guarantee the experiment will work, or even be safe.

Instead, the debate is about one of modern medicine's dirty little secrets: Doctors frequently prescribe one treatment over another without any evidence to know which option works best. There's no requirement that they tell their patients when they're essentially making an educated guess, or that they detail the pros and cons of each choice.

Researchers are supposed to outline all the risks when they study which commonly used option is best. But could that mislead patients into thinking research is riskier than their own doctor's best guess?

Federal health officials put that question to the public Wednesday, as they debate how strictly to regulate this type of research — a debate sparked by that study of premature babies who included Dagen Pratt of Kingwood, West Virginia

The tiniest preemies face serious risks, including death and disabilities.

Oxygen has been a mainstay of treating them, but doctors didn't know just how much to use. Too much causes a kind of blindness called retinopathy of prematurity. Too little can cause neurologic damage, even death. So hospitals used a range of oxygen, with some doctors opting for the high end and some for the low.

The Support study, conducted between 2005 and 2009, aimed to settle which end of that range was the best dose. It randomly assigned about 1,300 preemies at 23 hospitals to a lower or higher oxygen dose. To researchers' surprise, slightly more babies who got the lower dose died, a finding that has led to new standards for the care of preemies.

The problem: A government watchdog agency last spring ruled that researchers violated federal regulations that required them to spell out the risks of the study for parents. Nowhere in the consent forms that parents had to sign was death mentioned.

"This was a very, very important study to do," Dr. Jerry Menikoff, head of the Office for Human Research Protections, stressed Wednesday. "All we were asking for," he added, "is a couple of sentences to say there were risks."

He agreed with consumer advocates that a similar study in New Zealand phrased the issue more appropriately, saying the question is whether the lower dose "is safe and effective in reducing serious vision and lung problems without increasing mortality or neurodevelopmental disability."

But critics, including the head of the National Institutes of Health, argued that back in 2005, doctors didn't think the lower dose really posed a survival risk — the question was more about which dose did a good-enough job at saving their vision.

In fact, preemies who didn't enroll in the study — and got whatever range of oxygen their doctors deemed best — turned out to have a higher risk of death, said NIH Deputy Director Kathy Hudson.

Dr. John Lantos, a bioethicist at Children's Mercy Hospital in Kansas City, Missouri, knows that firsthand. His

**twin grandsons were born during the Support study but weren't given an opportunity to enroll. One died soon after birth. The other today is thriving but suffered severe retinopathy and has poor vision.**

"Nonvalidated therapy is often more dangerous than careful research," Lantos said, adding that the consent forms should make that clear as well. "Doctors just hate to say they don't know something. When they do say it, we should listen."

While the experts debated how to explain research risks, two families who traveled to Washington for the unusual meeting outlined a bigger hurdle: Reeling from the stress of having a vulnerable premie, they simply didn't understand that they were participating in an experiment. And they still haven't been told what dose of oxygen their children received, and it's impossible to say whether lingering health problems are a consequence of the study or of being extremely premature.

Yet, they now wish they hadn't participated.

"I unknowingly placed my son in harm's way," said Sharissa Cook of Attalla, Alabama, who wonders if vision problems experienced by her 6-year-old, Dreshan Collins, were caused by the study or from weighing less than 2 pounds at birth. "The only thing a mother wants is for her baby to be well."

Dagen's mother, Carrie, was more blunt with reporters: "Why is omitting information not considered lying?" she said. "We were told they would give her the best care every day."

## **Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Thursday, August 29, 2013 9:14 AM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]  
**Subject:** RE: Science magazine query - re SUPPORT issue

Thanks, Kerri. I think (b)(5). Renate is out today, so I'm ccing Amanda and Calvin.

Thanks,

John

### **John Burklow**

Associate Director for Communications and Public Liaison  
National Institutes of Health  
Building 1, Room 344  
(301) 496-4461 (phone)  
(301) 496-0017 (fax)  
[burklowj@od.nih.gov](mailto:burklowj@od.nih.gov)



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**From:** Childress, Kerri (NIH/NICHD) [E]  
**Sent:** Thursday, August 29, 2013 9:00 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]  
**Subject:** RE: Science magazine query - re SUPPORT issue

John: How would you like to handle this? Happy to assist in any way. Kerri

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, August 28, 2013 8:56 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** Re: Science magazine query - re SUPPORT issue

I just noted that Kerri was not on the cc: for this chain and needs to be.

Alan E. Guttmacher, M.D.  
Director

Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health

On Aug 28, 2013, at 8:04 PM, "Guttmacher, Alan (NIH/NICHD) [E]" <[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)> wrote:

Bob - want to query John Burklow?

Alan E. Guttmacher, M.D.

Director

Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health

On Aug 28, 2013, at 8:00 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

Let me know how to handle  
Thanks  
Rose

Sent from my iPhone

Begin forwarded message:

**From:** (b)(6)  
**Date:** August 28, 2013, 7:36:41 PM EDT  
**To:** <[rh298n@nih.gov](mailto:rh298n@nih.gov)>  
**Subject:** Science magazine query - re SUPPORT issue

Dear Dr. Higgins,

I attended the hearing at HHS today that stemmed from the SUPPORT controversy and spoke with your colleague Kathy Hudson, who is an old friend. She recommended I speak with you. I am trying to find out what impact this brouhaha is having on neonate studies funded by NIH. Please feel free to send this by your PAO officer if need be. I'm in a bit of a rush though - I need to write the story tomorrow (Thursday)

Thanks and best wishes

Arthur Allen  
freelance writer, Washington DC  
author, *Vaccine: the Controversial Story of Medicine's Greatest Lifesaver*  
(WW Norton, 2007); *Ripe: The Search for the Perfect Tomato*  
(Counterpoint, 2010)

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Rowe, Mona \(NIH/NICHD\) \[E\]](#); [Childress, Kerri \(NIH/NICHD\) \[E\]](#)  
**Date:** Thursday, August 29, 2013 9:09:31 AM  
**Attachments:** [Vaucher SUPPORT FU.pdf](#)

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ORIGINAL ARTICLE

## Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial

Yvonne E. Vaucher, M.D., M.P.H., Myriam Peralta-Carcelen, M.D., M.P.H.,  
Neil N. Finer, M.D., Waldemar A. Carlo, M.D., Marie G. Gantz, Ph.D.,  
Michele C. Walsh, M.D., Abbot R. Laptook, M.D., Bradley A. Yoder, M.D.,  
Roger G. Faix, M.D., Abhik Das, Ph.D., Kurt Schibler, M.D., Wade Rich, R.R.T.,  
Nancy S. Newman, R.N., Betty R. Vohr, M.D., Kimberly Yolton, Ph.D.,  
Roy J. Heyne, M.D., Deanne E. Wilson-Costello, M.D., Patricia W. Evans, M.D.,  
Ricki F. Goldstein, M.D., Michael J. Acarregui, M.D., Ira Adams-Chapman, M.D.,  
Athina Pappas, M.D., Susan R. Hintz, M.D., M.S.Epi., Brenda Poindexter, M.D.,  
Anna M. Dusick, M.D.,\* Elisabeth C. McGowan, M.D., Richard A. Ehrenkranz, M.D.,  
Anna Bodnar, M.D., Charles R. Bauer, M.D., Janell Fuller, M.D.,  
T. Michael O'Shea, M.D., M.P.H., Gary J. Myers, M.D.,  
and Rosemary D. Higgins, M.D., for the SUPPORT Study Group  
of the Eunice Kennedy Shriver NICHD Neonatal Research Network†

### ABSTRACT

#### BACKGROUND

Previous results from our trial of early treatment with continuous positive airway pressure (CPAP) versus early surfactant treatment in infants showed no significant difference in the outcome of death or bronchopulmonary dysplasia. A lower (vs. higher) target range of oxygen saturation was associated with a lower rate of severe retinopathy but higher mortality. We now report longer-term results from our pre-specified hypotheses.

#### METHODS

Using a 2-by-2 factorial design, we randomly assigned infants born between 24 weeks 0 days and 27 weeks 6 days of gestation to early CPAP with a limited ventilation strategy or early surfactant administration and to lower or higher target ranges of oxygen saturation (85 to 89% or 91 to 95%). The primary composite outcome for the longer-term analysis was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

#### RESULTS

The primary outcome was determined for 1234 of 1316 enrolled infants (93.8%); 990 of the 1058 surviving infants (93.6%) were evaluated at 18 to 22 months of corrected age. Death or neurodevelopmental impairment occurred in 27.9% of the infants in the CPAP group (173 of 621 infants), versus 29.9% of those in the surfactant group (183 of 613) (relative risk, 0.93; 95% confidence interval [CI], 0.78 to 1.10;  $P=0.38$ ), and in 30.2% of the infants in the lower-oxygen-saturation group (185 of 612), versus 27.5% of those in the higher-oxygen-saturation group (171 of 622) (relative risk, 1.12; 95% CI, 0.94 to 1.32;  $P=0.21$ ). Mortality was increased with the lower-oxygen-saturation target (22.1%, vs. 18.2% with the higher-oxygen-saturation target; relative risk, 1.25; 95% CI, 1.00 to 1.55;  $P=0.046$ ).

#### CONCLUSIONS

We found no significant differences in the composite outcome of death or neurodevelopmental impairment among extremely premature infants randomly assigned to early CPAP or early surfactant administration and to a lower or higher target range of oxygen saturation. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute; SUPPORT ClinicalTrials.gov number, NCT00233324.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Finer at the University of California, San Diego, Division of Neonatology, 200 W. Arbor Dr., San Diego, CA, 92013, or at nfiner@ucsd.edu.

Drs. Vaucher and Peralta-Carcelen contributed equally to this article.

\*Deceased.

†Members of the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network are listed in the Supplementary Appendix, available at NEJM.org.

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**E**XTRÊMELY PREMATURE INFANTS ARE AT high risk for death and neurosensory or developmental impairment in early childhood.<sup>1-3</sup> The risk of neurodevelopmental impairment increases with decreasing gestational age and greater severity of illness. Neurodevelopmental impairment is often a consequence of neonatal complications.<sup>4-12</sup> Although surfactant administration decreases the risk of death and bronchopulmonary dysplasia, randomized, controlled trials of various respiratory interventions have not shown significant reductions in mortality and morbidity or improvement in developmental outcomes.<sup>13-17</sup> We previously reported results of the multicenter, randomized, controlled Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), which involved extremely premature infants (from 24 to 27 weeks of gestation); treatment with noninvasive continuous positive airway pressure (CPAP) shortly after birth, as compared with early intubation and surfactant administration, did not reduce rates of death or bronchopulmonary dysplasia or other major morbidity at 36 weeks of postmenstrual age.<sup>18</sup>

Although oxygen supplementation is necessary for survival in many preterm infants, several studies have shown that it increases the risk of retinopathy of prematurity,<sup>19</sup> bronchopulmonary dysplasia,<sup>20,21</sup> periventricular leukomalacia,<sup>22</sup> and cerebral palsy.<sup>23</sup> Results from SUPPORT showed no significant difference in the composite outcome of death before discharge or severe retinopathy of prematurity among infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) versus a higher range (91 to 95%). However, in the lower-oxygen-saturation group, the risk of retinopathy of prematurity among infants who survived to discharge was decreased (8.6%, vs. 17.9% in the higher-oxygen-saturation group; relative risk, 0.52; 95% confidence interval [CI], 0.37 to 0.73;  $P < 0.001$ ) and the risk of death was increased (19.9% vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60;  $P = 0.04$ ).<sup>24</sup>

We now report the results of our longer-term follow-up of the infants in this study, assessing whether early, noninvasive CPAP with a limited ventilation strategy, as compared with early surfactant administration, and a lower, as compared with higher, target range of oxygen saturation would each decrease the incidence of death be-

fore assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age.

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## METHODS

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### STUDY DESIGN

SUPPORT was a randomized, controlled trial involving 1316 extremely preterm infants (gestational age, 24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009, who were enrolled at delivery at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days vs. 26 weeks 0 days to 27 weeks 6 days). Infants who were part of multiple births were randomly assigned, as a unit, to the same treatment group.

In the delivery room, the infants were randomly assigned to receive either CPAP immediately after delivery with a limited ventilation strategy, as described previously, if subsequent intubation was required, or intubation with surfactant administration within an hour after birth, followed by conventional ventilation.<sup>18</sup> Using a 2-by-2 factorial design, we also randomly assigned participants to a target oxygen-saturation range of 85 to 89% (lower-oxygen-saturation group) or 91 to 95% (higher-oxygen-saturation group); we used pulse oximeters that were specially designed to maintain blinding (see the Supplementary Appendix, available with the full text of this article at NEJM.org).<sup>24</sup>

The procedures for enrollment, intervention, and data collection have been reported previously.<sup>18,24</sup> The trial was approved by the institutional review board at each participating site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery. Two of the authors employed by RTI International vouch for the accuracy and completeness of the data and analyses reported, and the members of the SUPPORT subcommittee vouch for the fidelity of the trial to the study protocol (see the Supplementary Appendix).

## ASSESSMENTS

At 18 to 22 months of corrected age, surviving infants underwent a comprehensive neurodevelopmental assessment performed by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were evaluated annually for testing reliability. Cognitive function was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III); scores are assessed relative to a standardized mean ( $\pm$ SD) of  $100\pm 15$ , with higher scores indicating better performance.<sup>25</sup> The modified Gross Motor Function Classification System (GMFCS) was used to classify gross-motor performance, with scores ranging from 0 (normal) to 5 (most impaired).<sup>26</sup> Moderate-to-severe cerebral palsy was defined as a nonprogressive disorder with abnormal muscle tone in at least one arm or leg that was associated with abnormal control of movement or posture and a GMFCS score of 2 or higher.<sup>27,28</sup> Assessments of hearing impairment (defined as the inability to understand the oral directions of the examiner and to communicate, with or without hearing amplification) and visual impairment (defined as vision worse than 20/200) were based on examination and parental report.

Certified research staff collected demographic and neonatal-outcome data using standard definitions from the Neonatal Research Network. Demographic and outcome data included gestational age; birth weight; sex; status with respect to multiple gestation; race or ethnic group; and history of medical or surgical necrotizing enterocolitis (modified Bell's stage  $\geq 2$ , on a scale ranging from 1 to 3, with higher scores indicating greater severity of disease), intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia, late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia (physiological), and use of postnatal glucocorticoids. Socioeconomic variables included health insurance status, maternal marital status, maternal educational level, household income, language spoken at home, and status with respect to whether the child was living with biologic parents. Socioeconomic data were updated during the 18-to-22-month visit; these data were used if data from the neonatal period were not available.

## OUTCOMES

The prespecified primary composite outcome for this trial was death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age. This composite outcome was selected because infants who died before 18 months of corrected age could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the BSID-III of less than 70, a GMFCS score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment. Other prespecified outcomes at 18 to 22 months of corrected age were death and neurodevelopmental impairment. Exploratory secondary outcomes included the individual components of the neurodevelopmental-impairment assessment, levels of cognitive delay, and a comparison of outcomes within the higher and lower gestational-age strata.

## STATISTICAL ANALYSIS

The sample-size calculations were based on Neonatal Research Network data for infants born in the year 2000; the details have been reported previously.<sup>18,24</sup> Although the sample size for the study was estimated on the basis of hospital outcomes (i.e., death or bronchopulmonary dysplasia for the ventilation intervention, and death or retinopathy of prematurity for the oxygenation intervention), the final sample size was sufficient to detect an absolute reduction of 10 percentage points in the composite outcome of death or neurodevelopmental impairment, with the use of a two-sided significance level of 0.05, conservatively assuming an initial outcome rate of 55% in the surfactant and higher-oxygen-saturation groups and a 15% rate of loss to follow-up, as well as adjustment for familial clustering.

Data were entered on standard forms and were transmitted to RTI International, which stored, managed, and analyzed the data for the study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were performed with the use of chi-square tests for categorical variables and t-tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary

composite outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator used to calculate the frequency of each outcome was the number of children for whom status with respect to that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all 18-to-22-month outcomes were adjusted, as prespecified, for gestational-age strata, study center, and familial clustering (because infants who were part of multiple births were assigned to the same treatment group). Tests were conducted for the presence of statistical interaction between the two interventions by adding an interaction term to the models. To test the effect of characteristics that differed between the groups of children with and without follow-up, a sensitivity analysis using multiple imputation was conducted, in which missing values for the primary outcome were imputed on the basis of the treatment assignment, perinatal characteristics, and in-hospital outcomes.<sup>29</sup> Two-sided P values of less than 0.05 were considered to indicate statistical significance for all analyses; no adjustments were made for multiple comparisons.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

The primary composite outcome of death or neurodevelopmental impairment was determined for 93.8% of the children (1234 of 1316) enrolled in the trial (Fig. 1). A total of 258 children were known to have died before 18 to 22 months of age. Of the 68 children for whom a neurodevelopmental assessment was missing, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment was determined for 98.6% of all children seen (976 of 990); 14 children had an incomplete evaluation that precluded the assignment of a neurodevelopmental-impairment status. The follow-up rate and the mean corrected age at neuro-

developmental assessment were similar for all treatment groups (Table 1).

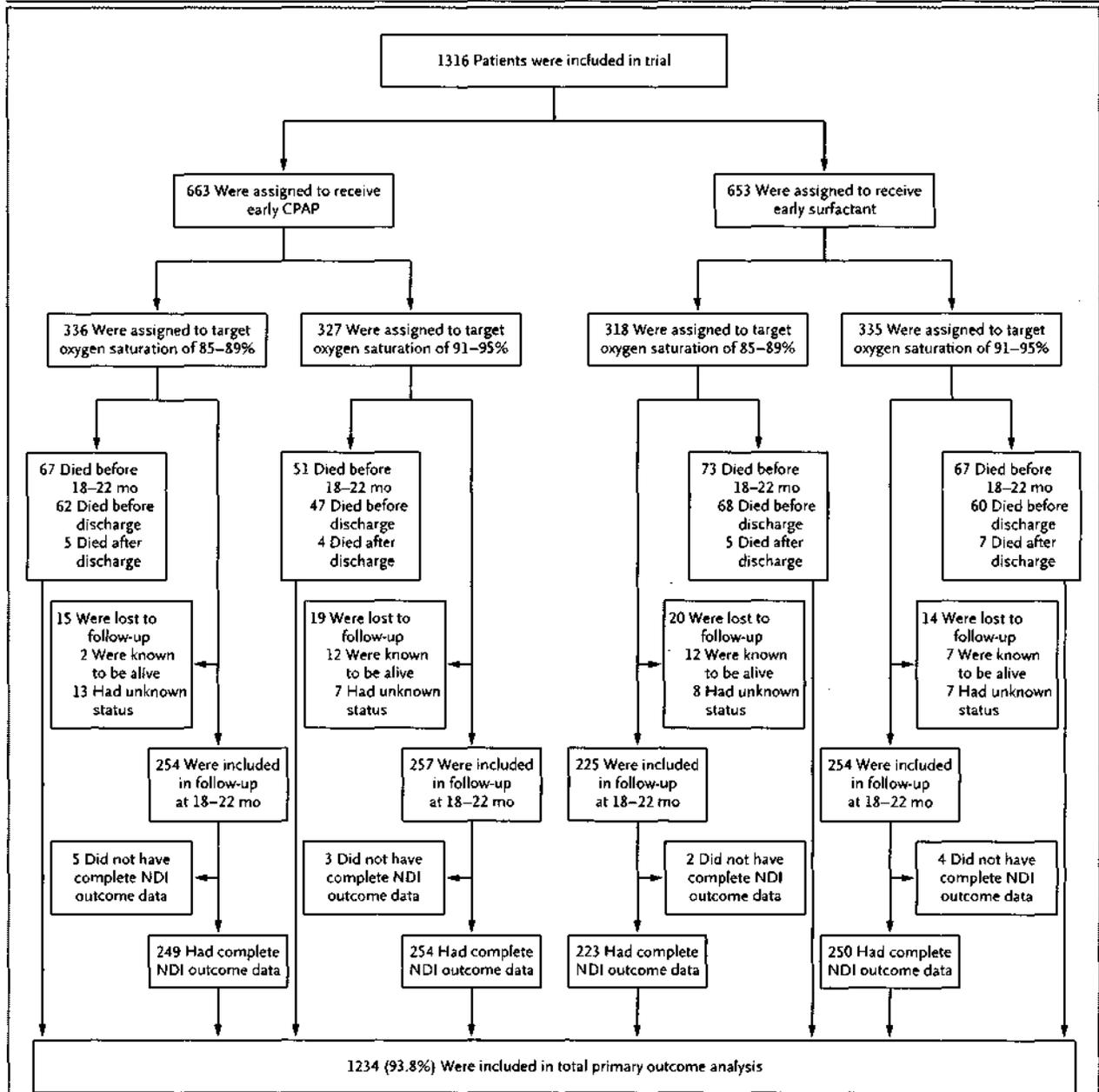
As compared with the mothers of the 990 children who underwent a neurodevelopmental assessment at 18 to 22 months of corrected age, the mothers of the 68 children who did not undergo an assessment were less likely to be married (47% vs. 31%,  $P=0.01$ ) and more likely to have only public health insurance (52% vs. 69%,  $P=0.008$ ). No other demographic or neonatal characteristics differed significantly between the groups.

The demographic and clinical characteristics of the follow-up population are summarized in Table 1 and in Table S1 in the Supplementary Appendix. Almost all mothers received antenatal glucocorticoids. At follow-up, there were more children who were small for their gestational age and more children with severe retinopathy of prematurity in the higher-oxygen-saturation group than in the lower-oxygen-saturation group. As compared with the surfactant group, children in the CPAP group were more likely to have had necrotizing enterocolitis and less likely to have been exposed to postnatal glucocorticoids. A total of 32% of the infants in the CPAP group were intubated in the delivery room; 65% of the infants in the CPAP group received surfactant with limited ventilation.

### PRIMARY OUTCOME

The frequency of the composite outcome of death or neurodevelopmental impairment did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups at 18 to 22 months of corrected age (Tables 2 and 3). Mortality before neonatal discharge accounted for 92% of the overall mortality observed by 18 to 22 months. Mortality did not differ significantly between the CPAP and surfactant groups but remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group. There were no significant differences in the primary outcome between treatment groups in subgroup analyses stratified according to gestational age at birth (Tables S2 and S3 in the Supplementary Appendix). The results of the sensitivity analysis using multiple imputations were virtually identical to the results of the analysis in which missing data were excluded (data not shown). There was no significant interaction be-

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL



**Figure 1. Enrollment, Randomization, and Outcomes.**

The primary composite outcome was determined for 93.8% of the enrolled infants. A total of 258 children were known to have died before 18 to 22 months of corrected age. Of the 68 children with a missing neurodevelopmental assessment, 33 were known to be alive. A neurodevelopmental assessment was performed at 18 to 22 months of corrected age for 990 of 1058 children (93.6%). The presence or absence of neurodevelopmental impairment (NDI) was determined for 98.6% of all children seen; 14 children had an incomplete evaluation that precluded the assignment of NDI status.

tween the two interventions with respect to the composite outcome of death or neurodevelopmental impairment or either of its components ( $P > 0.70$  for all comparisons).

**OTHER OUTCOMES**

The incidences of the individual components of neurodevelopmental impairment (BSID-III cognitive composite score of  $< 70$ , GMFCS score of  $\geq 2$ ,

**Table 1. Demographic and Clinical Characteristics of the Follow-up Cohorts.\***

Characteristic	CPAP (N=511)	Surfactant (N=479)	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=511)
Birth weight — g	849±186	852±193	858±186	844±192
Gestational age at birth — wk	26.3±1.1	26.3±1.1	26.3±1.1	26.2±1.0
Small for gestational age — no. (%)†	23 (4.5)	32 (6.7)	17 (3.5)‡	38 (7.4)
Male sex — no. (%)	256 (50.1)	266 (55.5)	240 (50.1)	282 (55.2)
Multiple birth — no. (%)	138 (27.0)	114 (23.8)	124 (25.9)	128 (25.0)
Maternal use of antenatal glucocorticoids — no. (%)	493 (96.5)	456 (95.2)	462 (96.5)	487 (95.3)
Cesarean section — no. (%)	352 (68.9)	315 (65.8)	332 (69.3)	335 (65.6)
Neonatal outcome — no./total no. (%)§				
Severe retinopathy of prematurity	62/479 (12.9)	58/434 (13.4)	38/442 (8.6)¶	82/471 (17.4)
Bronchopulmonary dysplasia	193/511 (37.8)	187/479 (39.0)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage of grade 3 or 4 or periventricular leukomalacia	70/510 (13.7)	46/478 (9.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis	56/511 (11.0)**	30/479 (6.3)	42/479 (8.8)	44/511 (8.6)
Late-onset sepsis or meningitis	167/511 (32.7)	154/479 (32.2)	155/479 (32.4)	166/511 (32.5)
Use of postnatal glucocorticoids	34/508 (6.7)**	55/476 (11.6)	41/477 (8.6)	48/507 (9.5)
Corrected age at follow-up — mo	19.9±2.4	20.1±2.7	19.9±2.4	20.2±2.7

\* Plus-minus values are means ±SD. There were no significant between-group differences, except as noted. Additional demographic characteristics of the cohorts are provided in Table S1 in the Supplementary Appendix. CPAP denotes continuous positive airway pressure.

† Infants who were small for gestational age were defined as those with a birth weight in less than the 10th percentile.

‡ P<0.01 for the comparison with the higher-oxygen-saturation group.

§ The comparisons of neonatal outcomes were adjusted for stratification factors (study center and gestational-age group) and familial clustering.

¶ P<0.001 for the comparison with the higher-oxygen-saturation group.

|| Assessment for bronchopulmonary dysplasia was performed at 36 weeks of postmenstrual age.

\*\* P<0.05 for the comparison with the surfactant group.

moderate or severe cerebral palsy, hearing impairment, and blindness) among surviving infants did not differ significantly between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups (Tables 2 and 3). Neither were there significant between-group differences in the individual components of neurodevelopmental impairment when the groups were stratified according to gestational age (Tables S2 and S3 in the Supplementary Appendix). However, in the lower-gestational-age stratum, mortality was higher in the surfactant group than in the CPAP group. Although the rates of severe retinopathy of prematurity and eye surgery were higher in the higher-oxygen-saturation group than in the lower-oxygen-saturation group, the rates of bilateral blindness, blindness of at least one eye, and other vision impairment

did not differ significantly between the groups at 18 to 22 months of corrected age (Table 4). There were no significant differences between the CPAP and surfactant groups or between the lower-oxygen-saturation and higher-oxygen-saturation groups in the rates of the composite outcome of death or individual neurodevelopmental-impairment components (data not shown), mean cognitive composite scores on the BSID-III, or the percentage of infants with cognitive composite scores of less than 80 points or less than 85 points (Table S4 in the Supplementary Appendix). Of the 976 children who were evaluated at 18 to 22 months of corrected age, 583 (60%) had normal status with respect to neuromotor, neurosensory, and cognitive development (with normal cognitive development defined as a BSID-III cognitive composite score of ≥85 points).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

Table 2. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the CPAP and Surfactant Groups.\*

Variable	CPAP	Surfactant	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	621/663 (93.7)	613/653 (93.9)	1.00 (0.97–1.03)	0.83
Death or NDI	173/621 (27.9)	183/613 (29.9)	0.93 (0.78–1.10)	0.38
Death before assessment at 18–22 mo of corrected age	118/643 (18.4)	140/638 (21.9)	0.83 (0.67–1.04)	0.10
NDI	55/503 (10.9)	43/473 (9.1)	1.16 (0.79–1.71)	0.44
BSID-III cognitive score <70†	36/502 (7.2)	36/472 (7.6)	0.95 (0.61–1.50)	0.84
GMFCS score ≥2‡	26/511 (5.1)	23/479 (4.8)	0.98 (0.57–1.69)	0.95
Moderate or severe cerebral palsy	21/511 (4.1)	19/479 (4.0)	0.93 (0.51–1.72)	0.82
Bilateral blindness	4/511 (0.8)	7/479 (1.5)	0.53 (0.16–1.78)	0.31
Hearing impairment	17/511 (3.3)	7/479 (1.5)	2.27 (0.96–5.37)	0.06

\* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic. NDI denotes neurodevelopmental impairment.

† Scores on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III), are assessed relative to a standardized mean ( $\pm$ SD) of  $100\pm 15$ , with higher scores indicating better performance.

‡ Gross-motor function was assessed by means of the modified Gross Motor Function Classification System (GMFCS), with scores ranging from 0 to 5 and higher scores indicating greater impairment.

## DISCUSSION

In this large, multicenter trial involving very-high-risk, extremely premature infants, we found no significant difference in the primary composite follow-up outcome of death before assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between infants randomly assigned to treatment with early CPAP and those assigned to early intubation and surfactant administration or between those randomly assigned to the lower-oxygen-saturation group and those assigned to the higher-oxygen-saturation group. Mortality did not differ significantly between the CPAP and surfactant groups, and mortality remained significantly higher in the lower-oxygen-saturation group than in the higher-oxygen-saturation group — findings that are consistent with our earlier results.<sup>18,24</sup> There were no significant differences between the CPAP and surfactant groups or between the higher-oxygen-saturation and lower-oxygen-saturation groups with respect to the frequencies among surviving infants of neurodevelopmental impairment and its components, including severe cognitive impairment (BSID-III

cognitive composite score, <70), moderate or severe cerebral palsy, moderate or severe motor impairment (GMFCS score, ≥2), hearing impairment, and bilateral blindness.

Recent trials have raised concern about using lower target ranges of oxygen saturation because of the possibility of increased mortality among extremely premature infants.<sup>21,30</sup> In SUPPORT, the risk of death during the initial hospitalization was increased among neonates randomly assigned to the lower-oxygen-saturation group, as compared with those assigned to the higher-oxygen-saturation group, and among neonates in the lowest gestational-age stratum, mortality was increased in the surfactant group as compared with the CPAP group. As previously reported, the causes of death did not differ significantly between the lower-oxygen-saturation and higher-oxygen-saturation groups.<sup>24</sup> Although significant differences in mortality persisted at 18 to 22 months of corrected age, these differences largely reflected the differences in mortality before hospital discharge. There are other ongoing studies of this matter that, once completed, could inform decisions.<sup>31</sup>

Severe retinopathy of prematurity may be as-

**Table 3. Rates and Relative Risks of Death before Assessment at 18 to 22 Months or Neurodevelopmental Impairment at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.\***

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Primary outcome determined	612/654 (93.6)	622/662 (94.0)	1.00 (0.97–1.03)	0.79
Death or NDI	185/612 (30.2)	171/622 (27.5)	1.12 (0.94–1.32)	0.21
Death before assessment at 18–22 mo of corrected age	140/633 (22.1)	118/648 (18.2)	1.25 (1.00–1.55)	0.046
NDI	45/472 (9.5)	53/504 (10.5)	0.87 (0.60–1.28)	0.49
BSID-III cognitive score <70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58–1.43)	0.69
GMFCS score ≥2	26/479 (5.4)	23/511 (4.5)	1.17 (0.68–2.01)	0.56
Moderate or severe cerebral palsy	20/479 (4.2)	20/511 (3.9)	1.00 (0.54–1.83)	>0.99
Bilateral blindness	5/479 (1.0)	6/511 (1.2)	0.90 (0.28–2.90)	0.86
Hearing impairment	12/479 (2.5)	12/511 (2.3)	1.16 (0.54–2.49)	0.70

\* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness were not adjusted for study center, owing to the small number of patients with this characteristic.

sociated with poor visual outcomes, even with treatment.<sup>32,33</sup> In this study, infants in the lower-oxygen-saturation group who survived to discharge had a lower incidence of severe retinopathy of prematurity (8.6%, vs. 17.9% in the higher-oxygen-saturation group).<sup>24</sup> Although eye surgery was significantly less frequent in the lower-oxygen-saturation group than in the higher-oxygen-saturation group, there were no significant between-group differences with respect to rates of unilateral and bilateral blindness, nystagmus, strabismus, or the use of corrective lenses. We did not collect detailed data on visual function at the 18-to-22-month visit.

The strengths of this study include the large initial sample, which provided sufficient power to detect a clinically significant difference in the prespecified outcome of death or neurodevelopmental impairment, and the high percentage of surviving infants who underwent a comprehensive, standardized neurodevelopmental evaluation at 18 to 22 months of corrected age.

The study also has several limitations. The requirement for antenatal consent, which is associated with enrollment bias, may limit generalizability.<sup>34,35</sup> In addition, the incidence of neurodevelopmental impairment in extremely premature infants in the present study was substantially lower than that previously reported by the Neonatal Research Network.<sup>36</sup> The present study used the BSID-III for cognitive assessment, where-

as previous Neonatal Research Network studies used an earlier edition, the BSID-II. Changes in the test design and standardization between the two editions may account for the lower incidence of neurodevelopmental impairment reported here.<sup>36</sup> Although the BSID-III scores in this study were higher than those previously reported for extremely premature infants, there were no significant differences between the treatment groups in this study.

Another limitation is the fact that the reported follow-up results are based on a single visit at 18 to 22 months of corrected age; other disabilities may not be evident until later in childhood. A subcohort of the SUPPORT study will be followed at school age to evaluate the longer-term neurodevelopmental outcome. Also, in comparing several secondary outcomes between pairs of treatments in this factorial-design trial (early CPAP vs. early surfactant treatment and lower vs. higher target ranges of oxygen saturation), we made no adjustments for multiple comparisons; appropriate caution should therefore be used in interpreting the reported results. Finally, differences in the neurodevelopmental outcome may have been blunted by the smaller difference in oxygen saturation between the higher-oxygen-saturation and lower-oxygen-saturation groups than was planned.<sup>24</sup>

In conclusion, there were no significant differences in the composite outcome of death before

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

**Table 4. Visual Outcome at 18 to 22 Months of Corrected Age in the Lower-Oxygen-Saturation and Higher-Oxygen-Saturation Groups.\***

Variable	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk (95% CI)	P Value
	<i>number/total number (percent)</i>			
Strabismus	46/478 (9.6)	41/510 (8.0)	1.20 (0.80–1.80)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89–3.69)	0.10
Eyes track 180 degrees	462/476 (97.1)	493/507 (97.2)	1.00 (0.98–1.02)	0.93
Corrective lenses for both eyes†	21/468 (4.5)	20/493 (4.1)	1.15 (0.63–2.10)	0.65
Blind with some function in both eyes†	3/450 (0.7)	2/475 (0.4)	1.57 (0.27–8.96)	0.61
Blind with no useful vision in both eyes†	2/449 (0.4)	4/477 (0.8)	0.54 (0.10–2.96)	0.48
Other abnormal eye finding‡	6/453 (1.3)	12/485 (2.5)	0.55 (0.21–1.46)	0.23
Blind in at least one eye	5/479 (1.0)	8/511 (1.6)	0.67 (0.22–2.02)	0.48
Eye surgery performed§	31/477 (6.5)	67/509 (13.2)	0.53 (0.35–0.78)	0.002

\* Relative risks and P values were adjusted for stratification factors (study center and gestational-age group) and familial clustering; analyses of blindness and other abnormal eye finding were not adjusted for study center, owing to the small numbers of patients with these characteristics.

† The reference group for relative risk was the group of children with vision that appeared to be normal in both eyes.

‡ Other abnormal eye finding was defined as an abnormality other than a condition requiring corrective lenses but not one severe enough for the child to be considered blind in that eye. Children whose eyes were classified in two different vision categories were included in the other-abnormal-eye-finding category.

§ Reasons for surgery are listed in Table S5 in the Supplementary Appendix.

assessment at 18 to 22 months or neurodevelopmental impairment at 18 to 22 months of corrected age between extremely preterm infants randomly assigned at delivery to early CPAP and those assigned to early intubation with surfactant administration or between infants assigned to lower oxygen saturation and those assigned to higher oxygen saturation. Early CPAP with a limited ventilation strategy can be considered as an alternative to early surfactant treatment, even in infants as immature as those at 24 weeks of gestational age. It is important to consider the

risk of death or neurodevelopmental impairment when deciding on oxygen-saturation targets in extremely preterm infants. Because mortality remained lower in the higher-oxygen-saturation group at the time of follow-up and there were no adverse visual or neurodevelopmental problems, lower oxygen-saturation targets cannot be recommended in these extremely preterm infants.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Department of Pediatrics, University of California at San Diego, San Diego (Y.E.V., N.N.F., W.R.), and the Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto (S.R.H.) — both in California; the Department of Pediatrics, University of Alabama at Birmingham, Birmingham (M.P.-C., W.A.C.); the Statistics and Epidemiology Unit, RTI International, Research Triangle Park (M.G.G.), the Department of Pediatrics, Duke University, Durham (R.F.G.), and Wake Forest University School of Medicine, Winston-Salem (T.M.O.) — all in North Carolina; the Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland (M.C.W., D.E.W.-C., N.S.N.), and the Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati (K.S., K.Y.) — both in Ohio; the Department of Pediatrics, Women and Infants Hospital, Brown University, Providence, RI (A.R.L., B.R.V.); the Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City (B.A.Y., R.G.F., A.B.); the Statistics and Epidemiology Unit, RTI International, Rockville (A.D.), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda (R.D.H.) — both in Maryland; the Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas (R.J.H.); the Department of Pediatrics, University of Texas Medical School at Houston, Houston (P.W.E.); the Department of Pediatrics, University of Iowa, Iowa City (M.J.A.); the Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta (I.A.-C.); the Department of Pediatrics, Wayne State University, Detroit (A.P.); the Department of Pediatrics, Indiana University School of Medicine, Indianapolis (B.P., A.M.D.); the Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston (F.C.M.); the Department of Pediatrics, Yale University School of Medicine, New Haven, CT (R.A.E.); the University of Miami Miller School of Medicine, Miami (C.R.B.); the University of New Mexico Health Sciences Center, Albuquerque (J.F.); and the Department of Pediatrics, University of Rochester Medical Center, Rochester, NY (G.J.M.).

OUTCOMES IN THE EARLY CPAP AND PULSE OXIMETRY TRIAL

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## **Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Burklow, John (NIH/OD) [E]  
**Sent:** Wednesday, August 28, 2013 4:02 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Subject:** Fw: Experts, families speak out on unethical study; police break up presser (Public Citizen press release)

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**From:** Sye, Tait (OS/ASPA)  
**Sent:** Wednesday, August 28, 2013 04:00 PM  
**To:** Daniels, Carla (HHS/ASPA/News Division); Gianelli, Diane M (OASH); Broido, Tara (HHS/OASH); Robinson, Michael J (HHS/ASPA); Baldauf, Sarah (OS/ASPA); Bradley, Ann (HHS/OASH); Burklow, John (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Salcido, Dori (HHS/ASPA)  
**Subject:** FW: Experts, families speak out on unethical study; police break up presser (Public Citizen press release)

Hi-

If you get media requests regarding this press release, please send to me.

(b)(5)

So far, only The Hill has asked for statement.

### **Statement regarding Public Citizen's press conference at HHS**

"To protect the visiting public and our federal personnel, HHS security policy restricts unannounced gatherings on federal property without prior permission. Public Citizen did not request permission to hold a press conference on federal property. The Federal Protective Services politely requested that Public Citizen move their press conference a short distance away from the front entrance of the building."

----- Forwarded message -----

**From:** Public Citizen Press Office <[press@citizen.org](mailto:press@citizen.org)>  
**Date:** Wed, Aug 28, 2013 at 3:40 PM  
**Subject:** Experts, families speak out on unethical study; police break up presser  
**To:** [mlillis@thehill.com](mailto:mlillis@thehill.com)

*Note: The U.S. Department of Health and Human Services called police to break up the press conference that Public Citizen held in front of the HHS entrance today. A blog post about the incident, with pictures and video, will be posted shortly on [citizenvox.org](http://citizenvox.org).*

### **HHS Must Stop Ongoing Unethical Trials on Premature Infants, Strengthen Ethical Standards for Human Research**

*'I Would Not Have Let My Baby in the Trial Had I Known of the Dangers,' Parent Says*

August 28, 2013

Contact: Angela Bradbery (202) 588-7741; Sam Jewler (202) 588-7779

WASHINGTON, D.C. – The federal government should halt all ongoing trials involving premature infants that are being conducted by the National Institutes of Health (NIH)-funded Neonatal Research Network until it can be determined that parents have been adequately informed of the dangers, Public Citizen said today at a press conference held outside the U.S. Department of Health and Human Services (HHS). In addition, HHS should strengthen – not weaken, as critics are pushing for – ethical and regulatory standards for human research.

“The fact that HHS is having a public discussion about this indicates that an enormous amount of pressure is being brought to bear by people who are trying to weaken the current standards of research with human subjects,” said Dr. Michael Carome, director of Public Citizen’s Health Research Group. “The debate goes to the heart of how research is conducted in the United States and could have far-reaching, negative implications if changes are made to weaken the ethical and regulatory standards by which trials are run. We cannot let that happen.”

Publicity generated by Public Citizen over an unethical trial, known as the SUPPORT study, prompted HHS to convene the unusual public forum at its headquarters. The meeting is designed to solicit comments from experts and the public about what risks should be disclosed to participants when research is focused on the so-called “standard of care” treatment given patients for a particular condition.

Since Public Citizen publicized the lack of adequate informed consent in the SUPPORT study, a controversy has raged in the scientific community over what kind of consent is needed in certain kinds of clinical trials.

In the SUPPORT study, which took place from 2005-2009 and was funded by the NIH, 1,316 premature infants were exposed to an increased risk of blindness, brain injury and death as researchers tested two experimental approaches for managing oxygen therapy.

The Office for Human Research Protections (OHRP), an office within HHS, determined earlier this year that the consent forms had significant deficiencies. In June, 45 experts signed a letter published in The New England Journal of Medicine denouncing the use of “seriously deficient” consent forms in the SUPPORT study that violated requirements for clinical trials.

Carrie and Shawn Pratt, parents of a baby enrolled in the trial, came from their home in Kingwood, West Virginia, to speak at the HHS meeting. They were accompanied by Dagen, now six, who required surgery early in life for an eye disease known as retinopathy of prematurity and suffers from cerebral palsy.

“The SUPPORT study looked good on paper,” Carrie Pratt said. “We were told that it wouldn’t hurt Dagen in any way. We were shocked to learn that the care she received was based not on what she needed but on what some protocol dictated. Had we known of the risks, we never would have agreed to have her be in the trial.”

“The SUPPORT study may represent the tip of the iceberg with the problems in contemporary medical research,” said Alice Dreger, Ph.D., professor of clinical medical humanities and bioethics at the Feinberg School of Medicine at Northwestern University, who spoke at the press conference. “Here, as so many times in the history of American medical research, the consent process failed.”

Added George Annas, JD, MPH, the William Fairfield Warren Distinguished Professor and Chair in the Department of Health Law, Bioethics & Human Rights at the Boston University School of Public Health, “A patient has a right to a physician who is duty-bound to protect their health interests. The research subject does not. ... At a minimum, the doctrine of informed consent requires the disclosure of any risks that could cause a

**reasonable person to reject the proposed medical treatment or research project.**

Last week, Public Citizen publicized the existence of another, similar trial that also poses known serious risks to premature babies, but researchers are not fully informing the parents about those risks when seeking consent. Called the Transfusion of Prematures (TOP) trial, it is designed to determine which of two strategies for treating anemia with blood transfusions is more likely to result in death or neurologic injury in extremely premature infants who develop anemia (low blood hemoglobin, which is found in red blood cells and carries oxygen to the body). The trial is just beginning.

Public Citizen is calling for: 1) HHS to immediately halt the TOP trial and direct OHRP to open an investigation into the trial; 2) OHRP to develop a plan to contact the parents of subjects already enrolled in the trial and provide them with full information about the risks, purpose and nature of the research; 3) an independent investigation of the HHS system for review and oversight of HHS-funded human subject research; and 4) a suspension of any other similar studies currently being funded by NIH or any other HHS agency.

It is unclear how much input HHS really wants; many people in Washington, D.C., are out of town in August because that is when Congress is out of session. In addition, HHS chose to hold the meeting on the 50th anniversary of the March on Washington.

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(202) 628-8523 - desk

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]  
**Subject:** Re: HHS videocast  
**Date:** Wednesday, August 28, 2013 11:51:08 AM

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My email is sporadic at best so I am not able to read on real time

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On Aug 28, 2013, at 11:32 AM, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov> wrote:

NRN did that analysis:

Rich WD; Gantz MG; Finer NN; Newman NS; Hensman AM; Hale EC; Auten KJ; Schibler K; Faix RG; Laptook AR; Yoder BA; Das A; Shankaran S; and the SUPPORT and Generic Database Subcommittees of the NICHD Neonatal Research Network. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. Pediatrics. 2012 Mar;129(3):480-484. Epub 2012 Feb 27.

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

From: Raju, Tonse (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 11:30 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

That is something that can be done. It might show (b)(5)

(b)(5)

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 11:27 AM  
To: Raju, Tonse (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis,

Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

Someone needs to point the (b)(5)

(b)(5)

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

From: Raju, Tonse (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 10:45 AM  
To: Willinger, Marian (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

These are the only federal folks. Hopefully we have neo folks later.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health  
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[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Willinger, Marian (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 10:44 AM  
To: Reddy, Uma (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

Too bad a (b)(5)

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

From: Reddy, Uma (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 10:41 AM  
To: Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

This is (b)(5)

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

From: Willinger, Marian (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 10:37 AM  
To: Raju, Tonse (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

I think the (b)(5)

(b)(5)

Sent: Wednesday, August 28, 2013 10:30 AM  
To: Reddy, Uma (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

There are lots of (b)(5)

(b)(5)

(b)(5)

Hopefully this will come out from other speakers coming next.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Reddy, Uma (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 10:28 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: HHS videocast

I can't believe (b)(5)

(b)(5)

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

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:52 AM  
To: Willinger, Marian (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

Click pause, then play again to reboot it.

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

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

From: Willinger, Marian (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:52 AM  
To: Tolivaisa, Susan (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

Yes- but no pix

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

From: Tolivaisa, Susan (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:52 AM  
To: Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

Sound's on!!! Yipeeeeeeeeeeeee

Best- Susan  
Ph: (301)435-6906  
FAX: (301)496-3790

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

From: Raju, Tonse (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:45 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

Now I lost the visuals, too.

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:44 AM  
To: Tolivaisa, Susan (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

And now the webcast seems to be stalled.

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

From: Tolivaisa, Susan (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:44 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
Subject: RE: HHS videocast

I sent an email saying there was no sound and at one point it sounded like there was

going to be a connection....but not yet.

Can't multitask either

Best- Susan

Ph: (301)435-6906

FAX: (301)496-3790

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

From: Archer, Stephanie (NIH/NICHD) [E]

Sent: Wednesday, August 28, 2013 9:43 AM

To: Willinger, Marian (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]

Subject: RE: HHS videocast

Going to go blind reading the closed captioning all day.

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

From: Willinger, Marian (NIH/NICHD) [E]

Sent: Wednesday, August 28, 2013 9:17 AM

To: Raju, Tonse (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]

Subject: RE: HHS videocast

At last cc is working now.

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

From: Raju, Tonse (NIH/NICHD) [E]

Sent: Wednesday, August 28, 2013 9:11 AM

To: Tolivaisa, Susan (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]; Willinger, Marian (NIH/NICHD) [E]

Subject: RE: HHS videocast

We all have the same problem. hope they fix it. I am reading closed caption.

Tonse N.K. Raju, MD, DCH

Chief, Pregnancy and Perinatology Branch Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health

Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

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

From: Tolivaisa, Susan (NIH/NICHD) [E]  
Sent: Wednesday, August 28, 2013 9:11 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; Hault, Ben (NIH/NICHD) [E]; Ileki, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]; Willinger, Marian (NIH/NICHD) [E]  
Subject: HHS videocast

I'm watching this on videocast but there is no sound...anyone else have the same problem?

Best -

Susan

Susan Tolivaisa

Clinical Trials Specialist

Maternal-Fetal Medicine Units Network & Maternal-Fetal Surgery Network

Eunice Kennedy Shriver National Institute of Child Health & Human Development

Pregnancy & Perinatology Branch / NIH

6100 Executive Blvd., Suite 4B03G

Rockville, MD 20852

[Susan.Tolivaisa@nih.gov](mailto:Susan.Tolivaisa@nih.gov)

Ph: (301)435.6906 FAX: (301)496.3790

<http://www.bsc.gwu.edu/mfmu>

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** "Michael Cotten, M.D."  
**Cc:** mball; Bell, Edward (Pediatrics); Higgins, Rosemary (NIH/NICHD) [E]; (apappas@med.wayne.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; dstevenson@stanford.edu; dwallace@rti.org; Ronald Goldberg, M.D.; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfcmd@aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); Ricki Goldstein, M.D.; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira\_adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yoltan; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Colaizy, Tarah T; Yvonne Vaucher; (Deanna Maffett@urmc.rochester.edu); (kwyynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Campbell, Donya D; Ellen Hale (ehale@emory.edu); Gauldin, Cheri; Georgia McDavid; Holly Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); Joanne Finkle, J.D.; Johnson, Karen (Pediatrics); Kimberley Fisher, Ph.D.; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Patty Luzader; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu); (kzaterka@rti.org); (mcunningham@rti.org); Petrie, Carolyn; newman@rti.org; Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org)  
**Subject:** RE: HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions  
**Date:** Wednesday, August 28, 2013 11:37:37 AM  
**Attachments:** HHS-OPHS-2013-0004-0021[1].pdf

For those that need it. Attached is the agenda for the meeting.

Stephanie Wilson Archer  
The Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
archerst@mail.nih.gov

**From:** Michael Cotten, M.D. [mailto:michael.cotten@duke.edu]  
**Sent:** Wednesday, August 28, 2013 10:05 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** mball; Bell, Edward (Pediatrics); Higgins, Rosemary (NIH/NICHD) [E]; (apappas@med.wayne.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; Michael Cotten, M.D.; dstevenson@stanford.edu; dwallace@rti.org; Ronald Goldberg, M.D.; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6)@aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); Ricki Goldstein, M.D.; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira\_adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yoltan; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Colaizy, Tarah T; Yvonne Vaucher; (Deanna Maffett@urmc.rochester.edu); (kwyynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Campbell, Donya D; Ellen Hale (ehale@emory.edu); Gauldin, Cheri; Georgia McDavid; Holly Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); Joanne Finkle, J.D.; Johnson, Karen (Pediatrics); Kimberley Fisher, Ph.D.; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Patty Luzader; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu); (kzaterka@rti.org); (mcunningham@rti.org); Petrie, Carolyn; newman@rti.org; Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org)  
**Subject:** Re: HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions

Awesome thanks!

Sent from my mobile device  
Dr. Michael Cotten

On Aug 28, 2013, at 9:50 AM, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov> wrote:

Try pausing and restarting the play.

---

**From:** mbball [mailto:mbball@stanford.edu]  
**Sent:** Wednesday, August 28, 2013 9:49 AM  
**To:** Bell, Edward (Pediatrics)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; (apappas@med.wayne.edu); (sahas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpointindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Lelf; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); 'ira adams-chapman'; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); 'Kim Yolton'; Marsha Gerdes (gerdes@email.chop.edu); 'Martha Colson'; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); 'Patrick Jones'; richard.ehrenkranz@yale.edu; 'Roy Heyne'; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); 'Susan Hintz'; Colazzy, Tarah T; Yvonne Vaucher; (Deanna Maffett@urmc.rochester.edu); (kwynn@upa.chop.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; 'Becky Bara'; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; 'Diana Vasil'; 'Diane Wilson'; Campbell, Donia D; Ellen Hale (ehale@emory.edu); Gaudlin, Cheri.; Georgia McDavid; Holly\_Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); 'Joanne Finkel'; Johnson, Karen (Pediatrics); 'Kimberley Fisher'; 'Leslie Wilson'; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Patty Luzader; 'Rachel Geller'; 'Rachel Geller'; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); 'Stephanie Wiggins'; Teresa Chanlaw (tchanlaw@mednet.ucla.edu); ' (kzaterka@rti.org)'; ' (mccunningham@rti.org)'; Archer, Stephanie (NIH/NICHD) [E]; 'Petrie, Carolyn'; 'newman@rti.org'; Jenna Gabrio (jgabrio@rti.org); 'Lewis-Evans, Amanda (alewis@rti.org)'  
**Subject:** Re: HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions

No, I was able to use the closed captions for a time but now even that's not running for me

On Aug 28, 2013, at 6:46 AM, "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> wrote:

Is the video streaming working for any of you?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, August 27, 2013 8:11 AM  
**To:** (apappas@med.wayne.edu); (sahas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpointindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Lelf; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan

(AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichji@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Volton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna\_Maffett@urmc.rochester.edu); (kwynn@upa.chop.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Gauldin, Cheri; Georgia McDavid; Holly\_Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Patty Luzader; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu) Cc: (kzaterka@rti.org); (mcunningham@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn; newman@rti.org; Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org)  
**Subject:** HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions

You may recall that HHS is holding a public meeting on **Wednesday, August 28, 2013** on the Protections of Human Subjects and Research Studying Standard of Care Interventions. The purpose of the meeting is to gather public perspectives to assist HHS in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects.

Additional information about the meeting can be found in the attached Federal Register notice, and, if you wish to follow the proceedings, HHS will be streaming the event via <http://www.hhs.gov/live>. The meeting begins at 9:00 a.m. and is scheduled to end at 5:00 p.m.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**Notice:** This UI Health Care e-mail (including attachments) is covered by the Electronic Communications Privacy Act, 18 U.S.C. 2510-2521, is confidential and may be legally privileged. If you are not the intended recipient, you are hereby notified that any retention, dissemination, distribution, or copying of this communication is strictly prohibited. Please reply to the sender that you have received the message in error, then delete it. Thank you.

**Public Meeting**  
**Matters Related to Protection of Human Subjects and**  
**Research Considering Standard of Care Interventions**  
**Wednesday, August 28, 2013**  
**Hubert H. Humphrey Building, Great Hall**

9:00 a.m. – 9:15 a.m.

**Opening Remarks**

Wanda K. Jones, DrPH  
Principal Deputy Assistant Secretary for Health  
U.S. Department of Health and Human Services (HHS)

**HHS Panel**

Jerry Menikoff, MD, JD  
Director, Office for Human Research Protections

Kathy Hudson, PhD  
Deputy Director for Science, Outreach, and Policy  
National Institutes of Health

Robert Temple, MD  
Deputy Center Director for Clinical Science  
Center for Drug Evaluation and Research  
Food and Drug Administration

9:15 a.m. – 12:00 p.m.

**Presentations & Panel Questions**

12:00 p.m. – 1:00 p.m.

**Lunch**

1:00 p.m. – 4:30 p.m.

**Presentations & Panel Questions**

4:30 p.m. – 4:45 p.m.

Brief summary of written comments

4:45 p.m. – 5:00 p.m.

**Closing Remarks**

Wanda Jones, DrPH  
Principal Deputy Assistant Secretary for Health  
U.S. Department of Health and Human Services

**From:** Willinger, Marian (NIH/NICHD) [E]  
**To:** Raju, Tonse (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]  
**Subject:** RE: Lantos  
**Date:** Wednesday, August 28, 2013 11:02:19 AM

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Yes but it took (b)(5)

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**From:** Raju, Tonse (NIH/NICHD) [E]  
**Sent:** Wednesday, August 28, 2013 11:02 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Ilekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tolivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NICHD) [C]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** Lantos

(b)(5)

Tonse N. K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
*Eunice Kennedy Shriver* National Institute of Child Health  
and Human Development, 6100 Executive Blvd, Room 4B03  
Bethesda, MD 20892-MS7510  
(For Courriers, instead of Bethesda, use Rockville, MD 20852)  
Phone: 301-402-1872; Fax 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

**From:** [Mondoro, Traci \(NIH/NHLBI\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Fw: HHS Talking Points: RE: FYI: HHS Public Meeting "Protection of Human Subjects and Standard of Care Research" and Public Citizen organization announcements  
**Date:** Wednesday, August 28, 2013 9:23:57 AM

---

Don't know if you received the talking points from HHS or not.

**From:** Carey, Curtis (NIH/NIAAA) [E]  
**Sent:** Wednesday, August 28, 2013 09:07 AM Eastern Standard Time  
**To:** Gibbons, Gary (NIH/NHLBI) [E]; Cook, Nakela (NIH/NHLBI) [E]; Shurin, Susan (NIH/NHLBI) [E]; Lauer, Michael (NIH/NHLBI) [E]; Pemberton, Victoria (NIH/NHLBI) [E]; Pearson, Gail (NIH/NHLBI) [E]; Gosselin, Teri (NIH/NHLBI) [E]; Hoots, W. Keith (NIH/NHLBI) [E]; Dimichele, Donna (NIH/NHLBI) [E]; Black, Jodi (NIH/NHLBI) [E]; Waclawiw, Myron A (NIH/NHLBI) [E]; Weinmann, Gail (NIH/NHLBI) [E]; Cooper-Arnold, Katharine (NIH/NHLBI) [C]; Kiley, James (NIH/NHLBI) [E]; Jones, Donna (NIH/NHLBI) [E]; Mondoro, Traci (NIH/NHLBI) [E]; Glynn, Simone (NIH/NHLBI) [E]  
**Cc:** Mockrin, Stephen (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]; Burrows, Stephanie (NIH/NHLBI) [E]; Wells, Connie (NIH/NHLBI) [E]; Earle, Melody (NIH/NHLBI) [E]; Le, Vicki (NIH/NHLBI) [E]; Lavine, Greg (NIH/NHLBI) [E]  
**Subject:** HHS Talking Points: RE: FYI: HHS Public Meeting "Protection of Human Subjects and Standard of Care Research" and Public Citizen organization announcements

**Provided below are the talking points from HHS. At this point we're expecting HHS and NIH OD to field media inquiries regarding the public meeting. We may still be asked to provide input on specific activities of TOP. Keith Hoots will be our spokesperson.**

**From:** Sye, Tait (OS/ASPA)  
**Sent:** Tuesday, August 27, 2013 5:46 PM  
**To:** Menikoff, Jerry (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Broido, Tara (HHS/OASH); Gianelli, Diane M (OASH); Burklow, John (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Bradley, Ann (HHS/OASH); Temple, Robert (FDA/CDER); Cox, Virginia (FDA/OC); Jefferson, Erica (FDA/OC); Blount, Aprile (FDA/CDER); Cannistra, Jennifer (OS/IOS); Adair, Geraldine (HHS/OGC)(CTR); Devaney, Stephanie (NIH/OD) [E]; Lee, Noelle C. (HHS/IOS); Hawkins, Jamar (HHS/OS); StithColeman, Irene E (HHS/OASH)  
**Cc:** Baldauf, Sarah (OS/ASPA); Bray, John P (OS/ASPA)  
**Subject:** Message guidance for tomorrow's meeting on protection of human subjects

Hi all-

I wanted to followup on yesterday's call and make sure we were all on the same page regarding messaging for tomorrow's meeting on protection of human subjects.

As there will be significant media interest and interview requests, our recommendation is for principals, in media interviews, to focus on the public meeting and not speculate on what will come next.

**Talking Points:**

(b)(5)

(b)(5)

**Hot Button QA:**

Q: When will OHRP release updated guidance regarding standard of care research?

A: The first step is to solicit comments and feedback from the public. After that, HHS will thoughtfully review the comments. There is no timetable set for releasing the updated guidance.

Q: Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

**Reporters who have registered to attend:**

David Brown, WP

Kim Skeen/Sharyl Atkinson, CBS Sunday Morning

Kim Barker, ProPublica

Meredith Wadman, Nature

Rachel Rettner, Live Science

Kathryn Foxhall/David Pittman, MedPage Today

**Reporters who will cover, likely watch livestream:**

Lauran Neergard, AP

Terese Delfino

Jeannie Baudman, BNA/Bloomberg

Tim Burton/John Rockoff, WSJ

Paul Basken, Chronicle of Higher Ed

**Public Citizen Press Conference Outside HHS**

Public Citizen has scheduled a press conference to occur outside HHS during the lunch break. The parents of one of the babies in the SUPPORT study will also be at the press conference. We recommend principals not respond/engage on the press conference, and pivot to the purpose of the public meeting.

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**From:** Carey, Curtis (NIH/NIAAA) [E]  
**Sent:** Tuesday, August 27, 2013 4:04 PM  
**To:** Gibbons, Gary (NIH/NHLBI) [E]; Cook, Nakela (NIH/NHLBI) [E]; Shurin, Susan (NIH/NHLBI) [E]; Lauer, Michael (NIH/NHLBI) [E]; Pemberton, Victoria (NIH/NHLBI) [E]; Pearson, Gail (NIH/NHLBI) [E]; Gosselin, Teri (NIH/NHLBI) [E]; Hoots, W. Keith (NIH/NHLBI) [E]; Dimichele, Donna (NIH/NHLBI) [E]; Black, Jodi (NIH/NHLBI) [E]; Waclawiw, Myron A (NIH/NHLBI) [E]; Weinmann, Gail (NIH/NHLBI) [E]; Cooper-Arnold, Katharine (NIH/NHLBI) [C]; Kiley, James (NIH/NHLBI) [E]; Jones, Donna (NIH/NHLBI) [E]; Mondoro, Traci (NIH/NHLBI) [E]; Glynn, Simone (NIH/NHLBI) [E]  
**Cc:** Mockrin, Stephen (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Ferrier, Robin (NIH/NHLBI) [E]; Burrows, Stephanie (NIH/NHLBI) [E]; Wells, Connie (NIH/NHLBI) [E]; Earle, Melody (NIH/NHLBI) [E]; Le, Vicki (NIH/NHLBI) [E]; Lavine, Greg (NIH/NHLBI) [E]  
**Subject:** FYI: HHS Public Meeting "Protection of Human Subjects and Standard of Care Research" and Public Citizen organization announcements

As you know, HHS is holding a Public Meeting from 9-5 Wednesday related to "Protection of Human Subjects and Standard of Care Research."

The meeting will be broadcast live online: <http://www.hhs.gov/live> Full details are available online: <http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/aug28public.html>

HHS ASPA is finalizing a public affairs guidance memo and talking points. NIH OD Office of Communications has the lead for our media relations. NHLBI and NICHD Communications are in supporting roles.

At this point we know that CBS News has a producer working on a story about the public meeting and it's possible that this meeting will generate additional attention.

Related to this Public Meeting, The organization Public Citizen announced they are going to be holding a news conference at noon Wednesday in front of the HHS building in D.C.  
<http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3967>

Some of you were previously involved in the response to Public Citizen's release on the SUPPORT study: <http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3859> and letter to Sebelius <http://www.citizen.org/documents/2111.pdf>.

Late last week they released a new statement on the TOP study: <http://www.citizen.org/pressroom/pressroomredirect.cfm?ID=3965> and letter to Sebelius <http://www.citizen.org/documents/2150.pdf>.

**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Confidential: Message guidance for tomorrow's meeting on protection of human subjects  
**Date:** Wednesday, August 28, 2013 8:23:03 AM

---

I hope (b)(5)

**Tonse N.K. Raju, MD, DCH**

Chief, Pregnancy and Perinatology Branch  
 Eunice Kennedy Shriver National Institute of Child Health and Human Development  
 National Institutes of Health  
 Phone: 301-402-1872, Fax: 301-496-3790  
 [rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, August 28, 2013 6:55 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** Fwd: Confidential: Message guidance for tomorrow's meeting on protection of human subjects

Sent from my iPhone

Begin forwarded message:

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
**Date:** August 27, 2013, 6:42:09 PM EDT  
**To:** "Bock, Robert (NIH/NICHD) [E]" <[bockr@exchange.nih.gov](mailto:bockr@exchange.nih.gov)>, "Guttmacher, Alan (NIH/NICHD) [E]" <[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)>, "Spong, Catherine (NIH/NICHD) [E]" <[spong@dir49.nichd.nih.gov](mailto:spong@dir49.nichd.nih.gov)>  
**Cc:** "Childress, Kerri (NIH/NICHD) [E]" <[kerri.childress@nih.gov](mailto:kerri.childress@nih.gov)>, "Rowe, Mona (NIH/NICHD) [E]" <[rowem@exchange.nih.gov](mailto:rowem@exchange.nih.gov)>, "Rush, Katie (NIH/NICHD) [E]" <[Katie.Rush@nih.gov](mailto:Katie.Rush@nih.gov)>  
**Subject:** RE: Confidential: Message guidance for tomorrow's meeting on protection of human subjects

Bob and everyone -

The statement below is (b)(5)

(b)(5)

Last week, Public Citizen raised concerns similar to SUPPORT in another NIH supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

A: HHS is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. Per OHRP's letter to UAB in June of this year, OHRP is postponing actions on studies involving similar designs to SUPPORT (standard of care in clinical research) until the process of producing appropriate guidance is completed.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal  
Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, August 27, 2013 5:57 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Rush, Katie (NIH/NICHD) [E]  
**Subject:** Confidential: Message guidance for tomorrow's meeting on protection of human subjects

Please see below. Best (b)(5)

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**From:** Fine, Amanda (NIH/OD) [E]  
**Sent:** Tuesday, August 27, 2013 5:47 PM  
**To:** Carey, Curtis (NIH/NIAAA) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Myles, Renate (NIH/OD) [E]  
**Subject:** FW: Message guidance for tomorrow's meeting on protection of human subjects

Hello-

Here is the guidance from HHS for tomorrow's meeting.

Thanks!

Amanda

---

**From:** Sye, Tait (OS/ASPA)

**Sent:** Tuesday, August 27, 2013 5:46 PM

**To:** Menikoff, Jerry (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Broido, Tara (HHS/OASH); Gianelli, Diane M (OASH); Burklow, John (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Bradley, Ann (HHS/OASH); Temple, Robert (FDA/CDER); Cox, Virginia (FDA/OC); Jefferson, Erica (FDA/OC); Blount, Aprile (FDA/CDER); Cannistra, Jennifer (OS/IOS); Adair, Geraldine (HHS/OGC)(CTR); Devaney, Stephanie (NIH/OD) [E]; Lee, Noelle C. (HHS/IOS); Hawkins, Jamar (HHS/OS); StithColeman, Irene E (HHS/OASH)

**Cc:** Baldauf, Sarah (OS/ASPA); Bray, John P (OS/ASPA)

**Subject:** Message guidance for tomorrow's meeting on protection of human subjects

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As there will be significant media interest and interview requests, our recommendation is for principals, in media interviews, to focus on the public meeting and not speculate on what will come next.

**Talking Points:**

(b)(5)



**Hot Button QA:**

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A: The first step is to solicit comments and feedback from the public. After that, HHS will thoughtfully review the comments. There is no timetable set for releasing the updated guidance.

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supported study, the Transfusion of Premature (TOP) trial. Do you think that trial should be suspended until new guidance is released?

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**Reporters who have registered to attend:**

David Brown, WP  
Kim Skeen/Sharyl Atkinson, CBS Sunday Morning  
Kim Barker, ProPublica  
Meredith Wadman, Nature  
Rachel Rettner, Live Science  
Kathryn Foxhall/David Pittman, MedPage Today

**Reporters who will cover, likely watch livestream:**

Lauran Neergard, AP  
Terese Delfino  
Jeannie Baudman, BNA/Bloomberg  
Tim Burton/John Rockoff, WSJ  
Paul Basken, Chronicle of Higher Ed

**Public Citizen Press Conference Outside HHS**

Public Citizen has scheduled a press conference to occur outside HHS during the lunch break. The parents of one of the babies in the SUPPORT study will also be at the press conference. We recommend principals not respond/engage on the press conference, and pivot to the purpose of the public meeting.

**From:** Walsh, Michele  
**To:** Tyson, Jon E  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkrantz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade Rich; mgantz@rti.org; "Duara, Shahnaz" (SDuara@med.miami.edu); nfiner@ucsd.edu; moshea@wfubmc.edu; Phelos, Dale; Laroja, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl\_dangio@umc.rochester.edu; Carlton, David E; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@outsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohts@salud.unm.edu); ronnie.quillet@umc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena (bsood@med.wayne.edu); Truog, William (MD); Uday Devaskar (UDEYASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Payne, Allison; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); Costello, Frank; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira.adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichji@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yoltan; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Jones, Patrick M; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna.Maffett@umc.rochester.edu); (kwynn@upa.chop.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gaudin, Cheri; Mcdavid, Georgia E; Holly Wadkins@umc.rochester.edu (Holly.Wadkins@umc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monka Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary.Jensen@umc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu); Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: John Lantos's statement for Network meeting Wednesday  
**Date:** Tuesday, August 27, 2013 7:03:38 PM

---

Hi jon we are at the restaruant Zaytinya corner of 9th and G. Are you able to come?

Sent from my iPhone

On Aug 26, 2013, at 6:53 PM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:

John agreed for his comments to OHRP (Wed morning) to be distributed to you. I think you will agree that it is very appealing and understandable to every audience we would want to reach.

<Lantos Comments for OHRP on CER - 8-23 (2).docx>

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**written consent of the person to whom it pertains, or as otherwise permitted by law.**

## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Rowe, Mona (NIH/NICHD) [E]  
**Sent:** Tuesday, August 27, 2013 3:48 PM  
**To:** Childress, Kerri (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Katie Rush; Kaeser, Lisa (NIH/NICHD) [E]; Glavin, Sarah (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** Fwd: NPR story

In case you didn't see already might have been in clips

Begin forwarded message:

**From:** "Devaney, Stephanie (NIH/OD) [E]" <[stephanie.devaney@nih.gov](mailto:stephanie.devaney@nih.gov)>  
**Date:** August 27, 2013, 12:30:20 PM MDT  
**To:** "Rowe, Mona (NIH/NICHD) [E]" <[rowem@exchange.nih.gov](mailto:rowem@exchange.nih.gov)>  
**Subject:** NPR story

<http://www.npr.org/blogs/health/2013/08/23/214800726/another-study-of-preemies-blasted-over-ethical-concerns>

For the second time in four months, the consumer group Public Citizen is alleging that a large, federally funded study of premature infants is ethically flawed.

Both complaints raise a big issue that's certain to get more attention beyond these particular studies: What's the ethically right way to do research on the validity of the usual care that doctors provide every day.

The U.S. Department of Health and Human Services will host an unusual forum on that question next Wednesday — stimulated by the sharp questions raised by Public Citizen.

This time around, the group is on a study called TOP, short for . The project hopes to enroll more than 1,800 severely premature infants to test when blood transfusions should be given to treat , a common and serious problem for tiny newborns.

The study randomly assigns preemies to one group that will get transfusions when their anemia is relatively mild or another that will wait until the disorder is severe. Researchers want to see which approach is better at reducing deaths and brain damage.

The study is very similar in approach to a 2010 trial called , which tested two different regimens for providing oxygen to 1,300 premature infants to see which one was less likely to cause blindness while avoiding death. That's not surprising, since both studies are being conducted by the same federally sponsored involving many of the same institutions.

As in its criticism of the earlier SUPPORT study, Public Citizen says the TOP investigators aren't informing parents of the risks to their infants compared to usual care, when preemies'

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance. **treatment is tailored to each situation. The group also criticizes the design of the TOP study, which does not set up a comparison group that receives usual, customized care.**

In a 20-page to Health and Human Services Secretary Kathleen Sebelius, Public Citizen calls for an immediate halt to the study "due to the serious deficiencies in the consent forms and unresolved questions about the ethics of the study design."

The National Institutes of Health is defending the study — just as National Institutes of Health Director Francis Collins in June SUPPORT.

The TOP study of anemia and transfusion timing "is an important study that adheres to the highest ethical and clinical standards," the NIH says in an email to Shots.

"NIH is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete and accurate information about the risks and benefits of participating in research," the statement continues.

It notes that the consent forms provided to parents at the 19 medical centers in the TOP study were all approved by their federally required Institutional Review Boards.

But that's one of the points of contention raised by Public Citizen's complaint.

The group says IRBs weren't given enough information to judge whether the proposed study is ethical. Its letter to Sebelius says ethics committees weren't told how much transfusion practices in the trial "deviate from the usual care ... and the risks thereby posed by these deviations."

The complaint also alleges that a committee set up to monitor the TOP study as it unfolds can't do the job because there's no comparison group of infants receiving "usual care." Such "" are charged with reviewing what happens to research subjects during the study, and are empowered to call a halt if some are doing significantly worse (or better) than others, or patients outside the study.

But the brunt of Public Citizen's criticism is that parents being asked to enroll their infants in TOP are not being told the whole story of the risks they might face. For instance, consent forms do not tell parents about the results of two previous studies of the when-to-transfuse question, which suggested that infants who got transfused late had higher incidence of death, brain injury and need for emergency transfusions.

Public Citizen notes that consent forms contain statements such as "This study does not carry any additional risk to your baby," "There are no known risks at this time to participation in this study," and risks "are exactly the same risks that exist in current medical practice."

The consumer group says parents should be told that if their infants are in the study, they will not get the individualized care tailored for their situation.

Ethicist of Boston University, who will speak at next week's forum, agrees on this point.

"You have to make sure parents understand what you're asking them to do," Annas tells Shots. "The primary thing is you're giving up your right to a physician who makes decisions based on what he or she thinks is in the best interest of your child rather than flipping a coin."

**The stakes in sorting out these issues are high. That's why Collins entered the fray in June, disavowing a ruling by an HHS ethics panel that criticized the SUPPORT study. Dozens of medical researchers and ethicists have also rallied around the SUPPORT investigators.**

**But an in this week's *Nature* strongly sides with the critics of SUPPORT and those who say full informed consent shouldn't be fudged when doing studies that test standard practices.**

**"Such 'standard of care' trials are likely to become more widespread," the editorial notes, "after being mandated in the 2010 health care law."**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Mondoro, Traci (NIH/NHLBI) [E]  
**Subject:** FW: John Lantos's statement for Network meeting Wednesday  
**Date:** Tuesday, August 27, 2013 9:54:44 AM  
**Attachments:** Lantos Comments for OHRP on CER - 8-23 (2).docx

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Monday, August 26, 2013 5:56 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Wade Rich; mgantz@rti.org; 'Duara, Shahnaz' (SDuara@med.miami.edu); nfiner@ucsd.edu; moshea@wfubmc.edu; 'Phelps, Dale'; Laroia, Nirupama; (Vivek.Narendran@cchmc.org); Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Frantz, Ivan; (suhas.kailapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl\_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler (kurt.schibler@cchmc.org); Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie\_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6)@aol.com; Gary Myers (gary\_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Jones, Patrick M; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; (Deanna\_Maffett@urmc.rochester.edu); (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Fortney, Christine; Gauldin, Cheri; Mcdavid, Georgia E; Holly\_Wadkins@urmc.rochester.edu (Holly\_Wadkins@urmc.rochester.edu); Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Linda Reubens; Monica Collins; Nancy Newman; Rachel Geller; Rachel Geller; Rosemary Jensen (Rosemary\_Jensen@urmc.rochester.edu); Stephanie Wiggins; Teresa Chanlaw

(tchanlaw@mednet.ucla.edu)

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** John Lantos's statement for Network meeting Wednesday

John agreed for his comments to OHRP (Wed morning) to be distributed to you. I think you will agree that it is very appealing and understandable to every audience we would want to reach.

## Risks of research versus the risks of non-validated therapy

John D. Lantos M.D.

Director, Bioethics Center, Children's Mercy Hospital, Kansas City, MO

Professor of Pediatrics, University of Missouri – Kansas City

I speak today as a grandfather.

Seven years ago, around the time that the SUPPORT trial started, my wife and I were blessed with twin grandchildren, Will and Sam. They were born at 23 weeks at a hospital that was participating in the SUPPORT study.

They were too premature to be eligible.

Sam died at 30 hours of age from respiratory failure. Will spent four months in the NICU and survived with severe retinopathy. After laser eye surgery, he has no peripheral vision and his central vision is 20/200 with glasses. But he is doing well – full of curiosity, laughter and love.

We didn't know about the SUPPORT study. Now, I wonder how our family would feel if the twins had been enrolled in that study.

Imagine that they had. If Sam then died as he died and Will developed retinopathy as he did, we likely would have blamed their bad outcomes on the study. We would have second-guessed the decision to enroll them. We would wonder whether they would have done better if the doctors had used their clinical judgment rather than a research protocol to decide how to treat them. If we later read that the consent forms were inadequate, we would

have been outraged. We would have felt like we had been deceived and our grandchildren were harmed as a result.

But imagine another scenario. Imagine that they had been eligible for the study and that their parents had been given consent forms that explained that the research risks included randomization, treatment by protocol, altered oximeters, and potential risks of death, eye disease, and neurodevelopmental problems. Imagine that, after reading of these risks, they decided not to enroll the babies in the study. And Sam then died as he died and Will developed eye disease as he did.

In that situation, we probably would not have been outraged. But we should have been. In that situation, sadly, no federal agency would have scrutinized the consent process and no advocacy groups would have called for public apologies. But they should. After all, the data show that babies like Sam who were in the study had higher survival rates than babies not in the study. Babies like Will who were in the study were less likely to have severe retinopathy. Babies who were offered individualized treatment did worse than those who were randomized and whose treatment followed precise protocols with careful monitoring for adverse events. Accurate consent forms should explain that those real and likely possibilities.

When consent forms overstate the risks of research, make no mention of the risks of conventional therapy, and don't say that research subjects might be better off than patients who are not in studies, they are not just inaccurate and misleading. They are dangerous. They are dangerous because such misleading inaccuracies scare patients away from safe, well-designed studies

and towards treatments with unknown – and often greater - risks. Patients are often harmed as a result.

Clinicians, investigators, IRBs, federal agencies like OHRP, and citizen advocacy groups should strive to protect patients from this insidious and predictable harm. To do this, they should insist that potential study subjects be given accurate information about the relative risks and benefits of both research and non-validated therapy. Only then can choices be truly informed choices.

Unfortunately, however, no federal agency protects babies from the risks of not being in research. No IRBs scrutinize the consent forms for the conventional therapy given to babies who choose not to be in studies. And no public advocacy group criticizes the cocky use of idiosyncratic clinical judgment.

Informed consent is the ethical cornerstone of both research and clinical practice. Patients – or parents of patients - have a fundamental right to information about proposed treatments, alternatives, risks, and benefits. This is true whether they are in research studies or not. On this, I believe, both admirers and critics of the SUPPORT study agree. But we disagree about where the greatest dangers lie.

In comparative effectiveness research, where none of the therapies are experimental, research studies are more likely to reduce risk than to increase it. Why? Because all of the risks of a well-designed comparative effectiveness study are also risks that are inevitably present for patients who

are not part of the study. I repeat – ALL of the risks of a well-designed CE study are also risks for patients who are not part of the study. If they were not, it would not be a well-designed study and should not have been approved in the first place.

The doctors and scientists who designed the SUPPRT study understood this. They did not think it was riskier to be in the study than not. So they didn't put this in the consent form. It is deeply ironic that these doctors, whose lives are devoted to taking care of premature babies, and who truly understand the complexities of such care, acknowledged that they didn't know which treatment was best. But bureaucrats in Washington and pundits in New York who have never set foot in a NICU much less cared for a 24 week preemie, insisted that those doctors did know – or should have known – what was best. Compounding the irony is the fact that the doctors, in their honest humility, did, in fact, know best - outcomes were better and the risks were lower for babies in the study.

Non-validated therapy is often more dangerous than careful research. That statement should be part of every consent form for every IRB approved comparative effectiveness trial. I hope that the federal regulations that come out of these hearings protect babies like Will and Sam from the misleading information that comes from outdated and erroneous ideas about the risks of research and about the safety of non-validated therapy. Our children deserve such protection.

**From:** Walsh, Michele  
**To:** Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Steering Committee Call 08/27  
**Date:** Tuesday, August 27, 2013 9:54:34 AM

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many of us will be flying to the HHS meeting. at 3pm so can not be on the call.

Rose: can you call me at home when you have a minute- (b)(6)

mw

---

**From:** Cunningham, Meg [mcunningham@rti.org]

**Sent:** Tuesday, August 27, 2013 8:33 AM

**To:** areynolds@upa.chob.edu; Athina Pappas; Avroy Fanaroff; Dan Ellsbury; David Carlton; dstevenson@stanford.edu; Eugenia Pallotto; mgantz@rti.org; Greg Sokol; Haresh Kirpalani; John Barks; jon.e.tyson@uth.tmc.edu; Keszler, Martin; Lina.Yossef@nationwidechildrens.org; Luc Brion; Meena Garg; Michael Cotten; nambalavanan@peds.uab.edu; rohls@salud.unm.edu; Ronnie Guillet; Satyan Lakshminrusimha; soraya.abbasi@uphs.upenn.edu; Sudarshan Jadcherla; barbara\_stoll@oz.ped.emory.edu; alaptook@WIHRI.org; Barbara Schmidt; Bell, Edward; Bill Truog; bpoindex@iu.edu; Carl D'Angio; adas@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; Leif Nelin; mcw3@cwru.edu; Pablo.Sanchez@UTSouthwestern.edu; RAP32@columbia.edu; sshankar@med.wayne.edu; Uday Devaskar; vanmeurs@leland.stanford.edu; Wallace, Dennis; Wally Carlo, M.D.

**Cc:** Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Gabrio, Jenna; Lewis-Evans, Amanda; Newman, Jamie; archerst@mail.nih.gov; Becky Brazeel; Brenda Vecchio; Garcia, Deborah; gonza025@mc.duke.edu; Heidi Kleinbart; Jim McBrien; jwaidne@emory.edu; Kristie Smiley; Imoore@med.wayne.edu; Nancy.M.Smith@uth.tmc.edu; Theresa Banker; VWILLI4@emory.edu; pamela.neville@duke.edu; Jennifer McDonald; Lisa Joo

**Subject:** RE: Steering Committee Call 08/27

Friendly reminder for today's call.

---

**From:** Cunningham, Meg

**Sent:** Friday, August 23, 2013 8:43 AM

**To:** 'areynolds@upa.chob.edu'; 'Athina Pappas'; 'Avroy Fanaroff'; 'Dan Ellsbury'; 'David Carlton'; 'dstevenson@stanford.edu'; 'Eugenia Pallotto'; 'Gantz, Marie (mgantz@rti.org)'; 'Greg Sokol'; 'Haresh Kirpalani'; 'John Barks'; 'jon.e.tyson@uth.tmc.edu'; 'Keszler, Martin'; 'Lina.Yossef@nationwidechildrens.org'; 'Luc Brion'; 'Meena Garg'; 'Michael Cotten'; 'Namasivayam Ambalavanan (nambalavanan@peds.uab.edu)'; 'rohls@salud.unm.edu'; 'Ronnie Guillet'; 'Satyan Lakshminrusimha'; 'soraya.abbasi@uphs.upenn.edu'; 'Sudarshan Jadcherla'; '[SCRN] Stoll, Barbara (barbara\_stoll@oz.ped.emory.edu)'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Barbara Schmidt'; 'Bell, Edward'; 'Bill Truog'; 'Brenda Poindexter (bpoindex@iu.edu)'; 'Carl D'Angio'; 'Das, Abhik (adas@rti.org)'; 'goldb008@mc.duke.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'Leif Nelin'; 'mcw3@cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'RAP32@columbia.edu'; 'sshankar@med.wayne.edu'; 'Uday Devaskar'; 'vanmeurs@leland.stanford.edu'; 'Wallace, Dennis'; 'Wally Carlo, M.D.'

**Cc:** Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Gabrio, Jenna; Lewis-Evans, Amanda; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); 'Becky Brazeel'; 'Brenda Vecchio'; 'Garcia, Deborah'; 'gonza025@mc.duke.edu'; 'Heidi Kleinbart'; 'Jim McBrien'; 'jwaidne@emory.edu'; 'Kristie Smiley'; 'Imoore@med.wayne.edu'; 'Michelle Smith (Nancy.M.Smith@uth.tmc.edu)'; 'Theresa Banker'; 'VWILLI4@emory.edu'; 'pamela.neville@duke.edu'; 'Jennifer McDonald'; 'Lisa Joo'

**Subject:** Steering Committee Call 08/27

Hi All,

Our next standing SC call is scheduled for Tuesday, August 27<sup>th</sup> at 3:00pm ET.

**Agenda**

1. Inositol update
2. PAS update
3. Budget update
4. Protocol primary outcomes
5. Clinicaltrials.gov responsible party
6. New business

Dial:

Within the USA: (b)(6)

or

Outside the USA: (b)(6)

Then, enter Participant Passcode: (b)(6)

Thanks!

Meg

*Meg Cunningham, CCRP  
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**From:** D'Angio, Carl  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions  
**Date:** Tuesday, August 27, 2013 8:25:13 AM

---

P.S. I spoke with Dale about the Thrasher issue. She's very aware of the issues and won't do anything precipitous, even if it means forgoing the opportunity.

*Carl*

Carl T. D'Angio, MD  
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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, August 27, 2013 8:11 AM  
**To:** (apappas@med.wayne.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; D'Angio, Carl; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); Guillet, Ronnie; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6)@aol.com; Myers, Gary; golds005@mc.duke.edu; Hailam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yoltan; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; Maffett, Deanna; (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Ball; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Gauldin, Cheri; Georgia McDavid; Wadkins, Holly; Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Reubens, Linda; Monica Collins; Nancy Newman; Patty Luzader; Rachel Geller; Rachel Geller; Jensen, Rosemary; Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)  
**Cc:** (kzaterka@rti.org); (mcunningham@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn; newman@rti.org; Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org)  
**Subject:** HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions

You may recall that HHS is holding a public meeting on **Wednesday, August 28, 2013** on the

**Protections of Human Subjects and Research Studying Standard of Care Interventions.** The purpose of the meeting is to gather public perspectives to assist HHS in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects.

Additional information about the meeting can be found in the attached Federal Register notice, and, if you wish to follow the proceedings, HHS will be streaming the event via <http://www.hhs.gov/live>. The meeting begins at 9:00 a.m. and is scheduled to end at 5:00 p.m.

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** D'Angio, Carl  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions  
**Date:** Tuesday, August 27, 2013 8:24:22 AM

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I'll probably see you there tomorrow!

*Carl*

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Director, Ethics Key Function, URM CTSI  
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[carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu)  
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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, August 27, 2013 8:11 AM  
**To:** (apappas@med.wayne.edu); (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; D'Angio, Carl; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sánchez (pablo.sanchez@nationwidechildrens.org); Polin, Richard; Robin Ohls (rohls@salud.unm.edu); Guillet, Ronnie; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (EMcGowan@tufts-nemc.org); Allison Payne; Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6)@aol.com; Myers, Gary; golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud.unm.edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Martha Colson; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher; Maffett, Deanna; (kwynn@upa.chob.edu); Aasma Chaudhary (aasma.chaudhary@uphs.upenn.edu); Angelita Hensman; Becky Bara; Bethany Bail; Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; Diana Vasil; Diane Wilson; Donia Campbell; Ellen Hale (ehale@emory.edu); Gaudin, Cheri,; Georgia McDavid; Wadkins, Holly; Joanne Finkel; Karen Johnson (karen-johnson@uiowa.edu); Kimberley Fisher; Leslie Wilson; Lijun Chen (Lijun.Chen@UTSouthwestern.edu); Reubens, Linda; Monica Collins; Nancy Newman; Patty Luzader; Rachel Geller; Rachel Geller; Jensen, Rosemary; Stephanie Wiggins; Teresa Chanlaw (tchanlaw@mednet.ucla.edu)  
**Cc:** (kzaterka@rti.org); (mcunningham@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Petrie, Carolyn; newman@rti.org; Jenna Gabrio (jgabrio@rti.org); Lewis-Evans, Amanda (alewis@rti.org)  
**Subject:** HHS Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions

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301-496-5575  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Devaney, Stephanie (NIH/OD) [E]  
**Sent:** Monday, August 26, 2013 9:45 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Carr, Sarah (NIH/OD) [E]  
**Cc:** Hudson, Kathy (NIH/OD) [E]  
**Subject:** Wednesday public meeting  
**Attachments:** Aug 28 Public Meeting Detailed Agenda \_23 August 2013.docx

Hi everyone -

Just wanted to remind you all that getting around downtown on Wednesday morning might be tricky with the Commemoration of the March on Washington taking place.

Also, as you all know, Kathy will be a panelist, along with Jerry Menikoff and Bob Temple from FDA, Wanda Jones will moderate. A detailed agenda is attached. Each presenter will have 7min to talk and then the panelists will have 5min for any response.

See you all on Wed.

Steph

**Public Meeting**  
**Matters Related to Protection of Human Subjects and**  
**Research Considering Standard of Care Interventions**  
**Wednesday, August 28, 2013**  
**Hubert H. Humphrey Building, Great Hall**

9:00 a.m. – 9:15 a.m.

**Opening Remarks**

Wanda K. Jones, DrPH  
Principal Deputy Assistant Secretary for Health  
U.S. Department of Health and Human Services (HHS)

**HHS Panel**

Jerry Menikoff, MD, JD  
Director, Office for Human Research Protections

Kathy Hudson, PhD  
Deputy Director for Science Outreach and Policy  
National Institutes of Health

Robert Temple, MD  
Deputy Center Director for Clinical Science  
Center for Drug Evaluation and Research  
Food and Drug Administration

9:15 a.m. – 12:00 p.m.

**Presentations & Panel Questions**

9:15 a.m. Michael Carome, MD  
Public Citizen (Washington, DC)

9:28 a.m. Sidney Wolfe, MD  
Public Citizen (Washington, DC)

9:41 a.m. Alice Dreger, PhD  
Northwestern University (Evanston, IL)

9:54 a.m. Lois Shepherd, JD  
University of Virginia Health System

10:07 a.m. George Annas, JD, MPH  
Boston University

10:20 a.m. Charles Natanson, MD

10:33 a.m. Vera Sharav  
Alliance for Human Research Protection (New York, NY)

10:46 a.m. Elisa Hurley, PhD  
Public Responsibility in Medicine and Research (Boston, MA)

10:59 a.m. John Lantos, MD  
Children's Mercy Hospital (Kansas City, MO)

11:12 a.m. Benjamin Wilfond, MD  
Seattle Children's Research Institute (Seattle, WA)

11:25 a.m. Robert Danner, MD

11:38 a.m. Nancy Kass, ScD  
Johns Hopkins Bloomberg School of Public Health (Baltimore, MD)  
11:51 a.m. Session wrap-up

12:00 p.m. – 1:00 p.m. **Lunch**

1:00 p.m. – 4:30 p.m. **Presentations & Panel Questions**

1:03 p.m. Jeffrey Drazen, MD  
New England Journal of Medicine & Harvard Medical School  
1:16 p.m. Peter Vasilenko, PhD  
Alion HRPP Accreditation Services (Washington, DC)  
1:29 p.m. Steven Joffe, MD, MPH  
University of Pennsylvania  
1:42 p.m. David Forster, JD, MA, CIP  
WIRB-Copernicus Group (Olympia, WA)  
1:55 p.m. David Magnus, PhD  
Stanford University (CA)  
2:08 p.m. Carl D'Angio, MD  
University of Rochester (NY)  
2:21 p.m. Jon Tyson, MD, MPH  
University of Texas Health Medical School  
2:34 p.m. Michele Walsh, MD, MS  
Case Western Reserve University (Cleveland, OH)  
2:47 p.m. Shawn Pratt  
Private Citizen (WV)  
3:00 p.m. Sharissa Cook  
Private Citizen (AL)  
3:13 p.m. Edward Champion, MD  
New England Journal of Medicine  
3:26 p.m. Michael McGinnis, MD, MPH  
Institute of Medicine (Washington, DC)  
3:39 p.m. Richard Platt, MD, MSc  
Harvard Medical School  
3:52 p.m. Ann Bonham, PhD  
American Association of Medical Colleges (Washington, DC)  
4:05 p.m. Robert Califf, MD  
Duke University (Durham, NC)  
4:18 p.m. Session wrap-up

4:30 p.m. – 4:45 p.m. Brief summary of comments submitted by 8/7/2013, by those who did not present today

4:45 p.m. – 5:00 p.m. **Closing Remarks**  
Wanda K. Jones, DrPH

## Blansfield, Earl (NIH/NICHD) [E]

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, August 26, 2013 7:02 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fwd: John Lantos's statement for Network meeting Wednesday  
**Attachments:** Lantos Comments for OHRP on CER - 8-23 (2).docx; ATT00001.htm

FYI

Sent from my iPhone

Begin forwarded message:

**From:** "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu>  
**Date:** August 26, 2013, 5:55:35 PM EDT  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "richard.ehrenkranz@yale.edu" <richard.ehrenkranz@yale.edu>, "Roger Faix (Roger.Faix@hsc.utah.edu)" <Roger.Faix@hsc.utah.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, Wade Rich <wrich@ucsd.edu>, "mgantz@rti.org" <mgantz@rti.org>, "Duara, Shahnaz' (SDuara@med.miami.edu)" <SDuara@med.miami.edu>, "nfiner@ucsd.edu" <nfiner@ucsd.edu>, "moshea@wfubmc.edu" <moshea@wfubmc.edu>, "Phelps, Dale" <Dale.Phelps@URMC.Rochester.edu>, "Laroia, Nirupama" <Nirupama.Laroia@URMC.Rochester.edu>, "(Vivek.Narendran@cchmc.org)" <Vivek.Narendran@cchmc.org>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "Frantz, Ivan" <Ivan.Frantz@childrens.harvard.edu>, "(suhas.kallapur@cchmc.org)" <suhas.kallapur@cchmc.org>, "Abbot Laptook (alaptook@wihri.org)" <alaptook@wihri.org>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)" <AnnaMaria.hibbs@cwru.edu>, "barbara\_stoll@oz.ped.emory.edu" <barbara\_stoll@oz.ped.emory.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "carl\_dangio@urmc.rochester.edu" <carl\_dangio@urmc.rochester.edu>, "Carlton, David P" <dpcarl@emory.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "dstevenson@stanford.edu" <dstevenson@stanford.edu>, "dwallace@rti.org" <dwallace@rti.org>, "Ed Bell (edward-bell@uiowa.edu)" <edward-bell@uiowa.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Greg Sokol (gsokol@iupui.edu)" <gsokol@iupui.edu>, "Haresh Kirpalani (KIRPALANI@email.chop.edu)" <KIRPALANI@email.chop.edu>, John Barks <jbarks@med.umich.edu>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Krisa Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, "Kristi Watterberg (kwatterberg@salud.unm.edu)" <kwatterberg@salud.unm.edu>, "Kurt Schibler (kurt.schibler@cchmc.org)" <kurt.schibler@cchmc.org>, "Luc Brion (luc.brion@utsouthwestern.edu)" <luc.brion@utsouthwestern.edu>, "Martin Keszler (mkeszler@wihri.org)" <mkeszler@wihri.org>, "mcw3@po.cwru.edu" <mcw3@po.cwru.edu>, "Meena Garg (mgarg@mednet.ucla.edu)" <mgarg@mednet.ucla.edu>, "Nelin, Leif" <Leif.Nelin@nationwidechildrens.org>, "Pablo.Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Polin, Richard" <rap32@mail.cumc.columbia.edu>, "Robin Ohls (rohls@salud.unm.edu)" <rohls@salud.unm.edu>, "ronnie\_guillet@urmc.rochester.edu" <ronnie\_guillet@urmc.rochester.edu>, Satyan Lakshminrusimha <slakshmi@buffalo.edu>, "Schmidt, Barbara (Neonatology)" <barbara.schmidt@uphs.upenn.edu>, "Seetha Shankaran" <sshankar@med.wayne.edu>, "Sood, Beena [bsood@med.wayne.edu]" <bsood@med.wayne.edu>, "Truog, William (MD)" <wtruog@cmh.edu>, "Uday Devaskar

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Cc: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>

**Subject: John Lantos's statement for Network meeting Wednesday**

John agreed for his comments to OHRP (Wed morning) to be distributed to you. I think you will agree that it is very appealing and understandable to every audience we would want to reach.

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Saturday, August 24, 2013 7:19 AM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** Fwd: CBS

Sent from my iPhone

Begin forwarded message:

**From:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>  
**Date:** August 24, 2013, 4:14:27 AM EDT  
**To:** "Finer, Neil" <nfiner@ucsd.edu>, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu>, "Mills, Meredith" <Meredith.Mills@uth.tmc.edu>  
**Cc:** "Colasurdo, Giuseppe N" <Giuseppe.N.Colasurdo@uth.tmc.edu>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Wootton, Susan H" <Susan.H.Wootton@uth.tmc.edu>, "Blanche (b)(6) @aol.com" <(b)(6) @aol.com>, "Walsh, Michele (Michele.Walsh@UHhospitals.org)" <Michele.Walsh@UHhospitals.org>, "Ed Bell (edward-bell@uiowa.edu) (edward-bell@uiowa.edu)" <edward-bell@uiowa.edu>, "Rose Higgins MD (higginsr@mail.nih.gov)" <higginsr@mail.nih.gov>, "Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu)" <wacarlo@uab.edu>  
**Subject:** Re: CBS

Neil.

I think it may be best if someone speaks with them rather than be seen as no one wants to do it. You may be the best person as you can claim no knowledge of the TOP trial.

Wally

-----Original message-----

**From:** "Finer, Neil" <nfiner@ucsd.edu>  
**To:** "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu>, "Mills, Meredith" <Meredith.Mills@uth.tmc.edu>  
**Cc:** "Colasurdo, Giuseppe N" <Giuseppe.N.Colasurdo@uth.tmc.edu>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Wootton, Susan H" <Susan.H.Wootton@uth.tmc.edu>, "Blanche (jontyson@aol.com)" <jontyson@aol.com>, "Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu)" <wacarlo@uab.edu>, "Walsh, Michele (Michele.Walsh@UHhospitals.org)" <Michele.Walsh@UHhospitals.org>, "Ed Bell (edward-bell@uiowa.edu) (edward-bell@uiowa.edu)" <edward-bell@uiowa.edu>, "Rose Higgins MD (higginsr@mail.nih.gov)" <higginsr@mail.nih.gov>  
**Sent:** Sat, Aug 24, 2013 07:56:55 GMT+00:00  
**Subject:** Re: CBS

Hi Jon and Meredith

I have been asked to be interviewed – and I think it would be appropriate for me to make the same response as indicated below

I am also worried about the newest of the Public Citizen charge about the Transfusion study so I would rather not be interviewed

Let me know if you all agree

Neil

From: <Tyson>, Jon Tyson <[Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu)<<mailto:Jon.E.Tyson@uth.tmc.edu>>>  
Date: Friday, August 23, 2013 10:37 PM  
To: "Mills, Meredith" <[Meredith.Mills@uth.tmc.edu](mailto:Meredith.Mills@uth.tmc.edu)<<mailto:Meredith.Mills@uth.tmc.edu>>>  
Cc: "Colasurdo, Giuseppe N" <[Giuseppe.N.Colasurdo@uth.tmc.edu](mailto:Giuseppe.N.Colasurdo@uth.tmc.edu)<<mailto:Giuseppe.N.Colasurdo@uth.tmc.edu>>>, "[kathleen.a.kennedy@uth.tmc.edu](mailto:kathleen.a.kennedy@uth.tmc.edu)<<mailto:kathleen.a.kennedy@uth.tmc.edu>>" <[kathleen.a.kennedy@uth.tmc.edu](mailto:kathleen.a.kennedy@uth.tmc.edu)<<mailto:kathleen.a.kennedy@uth.tmc.edu>>>, "Wootton, Susan H"

(b)(6)

>, "Wally Carlo

([wacarlo@uab.edu](mailto:wacarlo@uab.edu)<<mailto:wacarlo@uab.edu>>) ([wacarlo@uab.edu](mailto:wacarlo@uab.edu)<<mailto:wacarlo@uab.edu>>)" <[wacarlo@uab.edu](mailto:wacarlo@uab.edu)<<mailto:wacarlo@uab.edu>>>, Michele Walsh <[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)<<mailto:Michele.Walsh@UHhospitals.org>>>, Edward Bell <[edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)<<mailto:edward-bell@uiowa.edu>>>, Rosemary Higgins <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>>, Neil Finer <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)<<mailto:nfiner@ucsd.edu>>>

Subject: CBS

Meredith, I would suggest that we 1) provide the attached to provide background information providing views that may be helpful to CBS in interpreting the issues regarding informed consent and other regulatory issues related to SUPPORT and other comparative effectiveness trials ; 2) indicate that with the ongoing issues with litigation, we will be happy to respond in writing to their written questions but as they might expect have been advised not to speak on camera; and 3) we are not authorized to speak for and cannot presume to represent investigators at other universities, the Research Triangle International, or the NIH; these investigators and other NIH officials would need to speak for themselves.

**From:** Willinger, Marian (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Davis, Maurice (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Hoult, Ben (NIH/NICHD) [E]; Itekis, John (NIH/NICHD) [E]; Koso-Thomas, Marion (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Reddy, Uma (NIH/NICHD) [E]; Tollivaisa, Susan (NIH/NICHD) [E]; Williams, Sabrina (NIH/NIAID) [C]  
**Subject:** OHRP meeting Wednesday  
**Date:** Friday, August 23, 2013 4:57:53 PM

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**August 21, 2013 - Information on viewing the August 28, 2013 HHS Public Meeting on Protections of Human Subjects and Research Studying Standard of Care Interventions**

For those who cannot attend the August 28, 2013 HHS Public Meeting on the Protections of Human Subjects and Research Studying Standard of Care Interventions, HHS is providing an option to view the public meeting via live streaming technology. To view the HHS public meeting live on August 28, 2013, go to the HHS live streaming site at: [www.HHS.gov/live](http://www.HHS.gov/live), then hit the "Click to Play" arrow.

**From:** Tyson, Jon E  
**To:** Mills, Meredith  
**Cc:** Colasurdo, Giuseppe N; Kennedy, Kathleen A; Wootton, Susan H; Blanche (b)(6) @aol.com; Wally Carlo (wacarlo@uab.edu) (wacarlo@uab.edu); Walsh, Michele (Michele.Walsh@UHhospitals.org); Ed Bell (edward-bell@uiowa.edu) (edward-bell@uiowa.edu); Higgins, Rosemary (NIH/NICHD) [E]; Neil N Finer  
**Subject:** CBS  
**Date:** Friday, August 23, 2013 4:37:47 PM  
**Attachments:** QHRP CE research tyson Aug 23.docx

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Meredith, I would suggest that we 1) provide the attached to provide background information providing views that may be helpful to CBS in interpreting the issues regarding informed consent and other regulatory issues related to SUPPORT and other comparative effectiveness trials ; 2) indicate that with the ongoing issues with litigation, we will be happy to respond in writing to their written questions but as they might expect have been advised not to speak on camera; and 3) we are not authorized to speak for and cannot presume to represent investigators at other universities, the Research Triangle International, or the NIH; these investigators and other NIH officials would need to speak for themselves.

**HHS Public Meeting Regarding Research Assessing Standard of Care Interventions  
August 28, 2013**

**Comments Submitted by Jon Tyson, John Lantos, Kathleen Kennedy, and Susan Wootton**

*Our comments are focused on comparative effectiveness (CE) trials. CE trials compare outcomes for patients randomized to different treatment methods or management strategies used in clinical practice. CE trials differ from those for which current regulatory requirements for randomized trials were developed: trials comparing patients randomized to receive a new experimental intervention with control patients who receive conventional treatment or in some cases, a placebo or no treatment. The key difference is that CE trials have no "experimental" arm and no "control" arm and that the potential risks in one arm are the potential benefits of the other and vice versa.*

**1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?**

*This question and others that follow would be clearer and more meaningful if the term "standard of care" was removed or carefully limited to therapies demonstrated to be beneficial (as judged by criteria like the GRADE criteria<sup>1,2</sup> or those of the U.S. Preventive Services Task Force<sup>3</sup>). This term causes confusion when applied to unproven but routinely or commonly used therapies or treatment strategies which unfortunately make up the great majority of therapies used in clinical practice.<sup>4,5,6,7</sup> The fact that most treatments fall in this category highlights the pressing need to promote CE trials and a learning health care system.<sup>8,9,10</sup> To call one treatment or another "standard of care" misrepresents the very problem that policies for oversight of CE trials must solve. Such therapies would be better described by terms like "usual care" or "conventional treatment."*

*The first step for IRBs is to ask "Is the proposed trial justified?" CE trials are justified when there is inadequate evidence to determine the best treatment method for the patients to be studied. This decision may not be easy and may well require expertise in the clinical issue under investigation or in study design or interpretation.<sup>11</sup>*

*The trial should be deemed justified when the best available evidence indicates no clear overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied. CE trials should not be performed if there already is strong evidence from a proper systematic review of prior randomized trials<sup>12</sup> (indicating that one of the therapies to be studied is superior to the other). Such evidence may not be recognized without this kind of review. An exception might be considered if a compelling argument could be made that evidence from prior trials may not be generalizable to current practice. In the absence of prior trials, the need for a CE trial should be challenged if a well done cohort study has identified evidence of either strong benefit or hazard (a relative risk for an adverse outcome that is either  $\leq 0.10$  or  $\geq 10$ ) for one treatment method to be studied relative to the other.<sup>13</sup> Otherwise, observational studies may be quite misleading and are usually an inadequate basis to conclude that a CE trial is unwarranted.*

*Therapies are ordinarily first evaluated in efficacy trials (to assess therapies under ideal or restricted circumstances). Therapies found to be beneficial in efficacy trials then need evaluation in effectiveness trials (to assess therapies in routine clinical circumstances). Therapies that are clearly beneficial but quite expensive may also be considered as appropriate for CE trials. In such situations, the trials would be designed to assess whether such therapies are reasonably cost effective for general use or limited use in highly selected centers or patient populations.*

**a. Under what circumstances should an IRB consider those to be risks that may result from the research?**

*The Common Rule states that the risks of research are the incremental risks from participation in research, as compared to the risks that would be experienced without study participation. In a legitimate CE trial the treatments under investigation are already used in clinical practice, and there is no predictable or reasonably foreseeable overall difference in their risks (relative to the benefits) as assessed from the best available evidence. So any differences in outcomes observed in the trial result from unpredictable treatment risks or baseline differences in disease severity and are not from the risks of the research itself.*

*Systematic reviews of outcomes for patients in well-designed RCTs provide no evidence that participation in a trial, compared to non-participation in the trial, increases the actual risks of adverse outcomes identified at the completion of the trial.<sup>14,15</sup> Thus, there is no empiric basis to assume that CE trials compromise the outcome of participants for the benefit of future patients. Physicians who conduct such trials are committed to the welfare of the patients. If they knew the best treatment for these patients, they would provide it. In some trials, patient risk may be reduced by the investigators' efforts to most effectively provide the therapies under investigation, to optimize the patient's supportive care and clinical monitoring, and to minimize and more quickly identify and address treatment hazards or disease complications than would occur in clinical practice.*

**b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?**

As noted by OHRP, the IRB is to consider research risks to be only the risks and benefits that may result from the research (as distinguished from those that participants would incur even if not participating in research). In many studies, those risks are easily identifiable. They include risks from extra blood drawing, biopsies, or other procedures imposed by the study that would not ordinarily be done in routine clinical care. The IRB should consider these risks to be related to the research. They should not consider the risks of being assigned to one arm or the other of a CE trial to be a risk of research, even if, as a result of the study, the chances that a particular patient receives one therapy or another may be different if they are in the study compared to if they are not.

The specific risks of the individual therapies under investigation are likely to differ. However, the IRB's agreement that the trial is justified indicates agreement that there is no predictable overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied as judged from the best available evidence.

**c. What type of evidence should an IRB evaluate in identifying these risks?**

The IRB should evaluate the methodologically strongest relevant evidence in assessing the need for the trial and in identifying the specific risks of the individual therapies under investigation. The investigators should reference and describe the findings of any systematic review of all relevant randomized trials (particularly the well performed reviews of the Cochrane Collaboration). Unless refuted by rigorous randomized trials, evidence about treatment risks from well performed cohort or case-control studies may also be considered

Even in randomized trials, the available evidence is not always easily interpreted, particularly when the proposed trial involves populations or circumstances not previously assessed or when offsetting benefits and hazards or evidence of subgroup differences or treatment heterogeneity are identified in prior trials. As noted above, criteria like the GRADE criteria or those of the Preventive Task Force may help in evaluating and integrating the available evidence. The AGREE II criteria<sup>16,17</sup> may be helpful in evaluating the evidence underlying practice guidelines. IRBs, like investigators and clinicians, will need to stay abreast of methods being developed or used to evaluate when the treatment hazards outweigh the benefits for individual patients or patient subgroups.<sup>18,19</sup>

**2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?**

**a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?**

We see a number of issues that should be considered for these questions:

**A. The available evidence about potential treatment hazards.** Potential risks that can be considered to be reasonably foreseeable would include a) biologically plausible treatment hazards that have not been well assessed in clinical studies, and b) hazards that have been evaluated in a systematic review of relevant clinical trials or in the absence of such a review, in one or more clinical trials or well performed cohort studies and found to marginally or significantly associated with the treatment ( $p \leq 0.10$ ). In accordance with the principles of evidence-based medicine, investigators should not be required to list on a consent form all possible hazards or hazards that are not close to significant ( $p > 0.10$ ) in systematic reviews or in well performed clinical trials or cohort studies. To deem such potential hazards as "reasonably foreseeable" would require investigators to list almost any hazard that that could be considered minimally plausible despite evidence to the contrary. This might more often mislead than inform potential research participants or their surrogates. Listing all potential minor or rare hazards would also distract attention from hazards of greater importance to patients.

Foreseeable treatment risks often do not include some or many of the secondary outcomes listed in the protocol. Investigators often specify exhaustive lists of secondary outcomes for CE trials to ensure that all potentially important outcomes are carefully monitored and recorded and that unexpected observed differences are accepted by reviewers as "pre-specified" outcomes. Whether these should be listed as risks hinges on the available evidence as noted above.

**B. Risk disclosure with competing outcomes.** From the public health perspective, the most important CE studies assess primary outcomes important to patients, e.g., heart attacks or strokes, rather than short-term changes in things like blood pressure or laboratory tests. Study participants often must be monitored for long periods of time to evaluate these outcomes. If the participants are at high risk for death, as would be the case for elderly adults or small premature infants, some or many may die before they have to opportunity to develop such outcomes. In this circumstance, death is thus a competing outcome that prevents the identification of other adverse outcomes. For this reason, it is often prudent to

include death in the primary outcome (e.g. heart attack, stroke, or death) even though the investigators may have no reason to think that the different treatments would result in a difference in mortality. Including death in the primary outcome can prove to be particularly fortunate if, as sometimes happens, one of the treatments under investigation is associated with an increased mortality rate despite reducing other adverse outcomes like heart attacks or strokes.<sup>20</sup> However, the inclusion of death in the primary outcome should not be assumed to indicate that a higher mortality is foreseeable based on the best available evidence or should be noted on the consent form as a foreseeable risk for either treatment group.

**C. A need for individualized consent forms?** It might be argued that incremental risks and benefits of study participation should be disclosed in comparison to the treatment that each individual participant would otherwise receive. However, this approach is unlikely to be feasible. Clinicians' treatment preferences often vary by provider, may be variable or change over time, and may not be known at enrollment. Efforts to individualize the consent form would lead to troublesome differences in the forms within and across different study sites. For these reasons, the risks and benefits of participation cannot be listed in separate "risks" and "benefits" sections of a typical consent form template. The "risks" of one study strategy (higher risk of xxx) are "benefits" (lower risk of xxx) for the other strategy. A better approach would be to inform subjects in a straightforward manner of the prevailing practice variation and explain why researchers believe that randomization is appropriate. This information would be the same for all subjects and would be consistent with the IRB's approval of the study as a legitimate CE trial.

**4. The need to develop better and more uniform approaches to risk disclosure for use of unproven therapies in both research and clinical practice.** This need requires further study of such issues as the wants, needs, and comprehension of patients (or their surrogates) in routine and emergent circumstances; the effects of differing approaches to risk disclosure (including placebo effects<sup>21</sup>); and factors that can augment the validity of informed consent. It is difficult to see how any ethical principles including respect for persons, beneficence, or justice justify a different level of risk disclosure in clinical practice and clinical research for patients receiving the same unproven treatment method. There also seem to be no data to indicate that well informed patients support this double standard.

**3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk?**

Randomization should not be considered to increase risk in legitimate CE trials because:

A. As discussed above, randomization to alternative treatment methods in such trials has no foreseeable effect on treatment risks for participants in the trial.

Randomization is simply a tool to avoid differences in baseline risk between treatment groups that are a notorious cause of confounding in observational studies comparing different therapies. It thus reduces the possibility of misleading results and erroneous conclusions but has no effect on the risks of the treatments provided.

In many clinical circumstances, there is inadequate relevant evidence to determine which of a number of commonly used treatments is preferable. In those circumstances, the treatment that is chosen will depend on happenstance and vary as a result of such factors as where the patient happens to be treated, who the treating physician happens to be, and what his or her treatment preferences happen to be. Those treatment preferences may reflect the considerations of an extremely dedicated, well informed, and appropriately uncertain physician. Alternatively, it may be based on the physician's vague recall of the relevant research, a clinical anecdote, a casual conversation with colleagues, or a recent visit from a drug company representative. It may be a combination of these factors. The net result, in the absence of good evidence from good clinical trials, is a decision that at best is similar to a mental flip-of-the-coin

B. The unfounded assumption that clinical trials increase risk leads to associated regulatory requirements to warn patients of dubious or non-existent risks. This may inadvertently harm patients by disincentivizing proper testing in the most rigorous feasible CE research and by incentivizing clinical use of unproven and possibly hazardous therapies.

As indicated below, this effect can have major serious adverse consequences that should be carefully considered.

**Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?**

Providing the CE trial is justified, waiver would be allowable in some circumstances,<sup>22,23,24,25</sup> and well justified in urgent or emergent circumstances when valid consent cannot be reasonably obtained and when treatment delays to obtain consent (~ 1 hour, if not longer, in many trials) would be expected to alter the treatment benefits or hazards. This approach would expand the current criteria to allow waiver of consent when the treatment is not considered potentially life-saving and remove the requirement for community participation in these circumstances. Patients receiving proven emergency therapies benefit from prior studies, and their participation in well justified CE research are needed to further

improve outcomes. Requiring consent in these circumstance can A) increase the morbidity or mortality of trial participants;<sup>26,27</sup> B) result in erroneous conclusions that adversely affect the care and outcome of a very large number of future patients; C) delay completion of a valid trial and dissemination of truly beneficial therapies or abandonment of truly harmful therapies in clinical practice. Requiring consent in these circumstances violates the principle of beneficence and arguably, also respect for persons and justice.

Public understanding of CE research in these circumstances could be promoted by including potential study participants in the process of study design as well as by rigorous efforts to explain to participants who have been enrolled in trials of emergency therapies without their consent - in as timely manner as possible - the rationale for the study and the reasons why they or their loved one was enrolled. At that time, investigators should also seek the patient's consent to continue in the trial or to allow use of their data.

Whatever disclosure and consent procedures are required for CE trials, we would urge that they should be similar for all patients receiving the same unproven therapy whether as part of routine clinical care, a prospective observational study, or a randomized trial. As we have argued elsewhere,<sup>29</sup> consent procedures deserve reconsideration for clinical as well as research use of unproven therapies, particularly new unproven therapies. As Fost has emphasized, it is not plausible to presume that a patient would want a therapy never properly tested for safety or efficacy with no prior review, but would object to the same treatment being given with all the safeguards of a controlled trial. The current double standard for both risk disclosure and written consent inadvertently discourages proper testing, encourages clinical administration of unproven therapies, and contributes to the all-too-common problem that unproven therapies are widely used for years or even decades before they are rigorously evaluated and found to be ineffective or harmful.<sup>5,28,29,30</sup>

#### **4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions?**

The uncertainty about risk is influenced by the quality of the prior research, the *p* values and confidence intervals for the measures of treatment effect (relative risk, risk difference, and number needed to treat or number needed to harm), and in some studies, Bayesian estimates of the probability of specific treatment effects. The discussion above indicates how this uncertainty may be judged in addressing these questions. To the extent feasible, the level of uncertainty should be conveyed to study subjects, but optimal methods have not been developed for conveying these complex concepts to patients with variable skills in literacy and numeracy.

#### **What if the risk significantly varies within the standard of care?**

As noted above, the trial is not justified if the relationship of risks to benefits has been shown to be more favorable in one treatment group than the other(s). Suggestions are detailed above for disclosing risks and benefits or advantages and disadvantages of different study strategies that are within the range of common practice.

#### **5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases risk of harm, or is it necessary that there be published studies identifying the risk?**

It is unclear what is meant by "documented beliefs." However, the beliefs within the medical community about an intervention can vary widely, particularly if they have not been well assessed in randomized trials. As evident from the long unfortunate history indicating the need for rigorous trials to assess oxygen administration to premature infants,<sup>31,32</sup> the evidence supporting the treatment is more important than the level of belief among some or many physicians.

As noted above, potential treatment risks need not be disclosed if they were well assessed and shown to have no association in relevant clinical trials of these therapies, or in the absence of these trials, in well performed cohort studies. Biologically plausible potential treatment hazards that have not been assessed in clinical studies should ordinarily be disclosed if they would be of concern to a sizable proportion of patients.

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**Susan H. Wootton, MD**  
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<sup>29</sup> J. Tyson, "Use of unproven therapies in clinical practice and research: How can we better serve our patients and their families?," *Seminars in Perinatology* 19 (1995): 98-111.

<sup>30</sup> I. Chalmers, "Regulation of Therapeutic Research is Compromising the Interests of Patients," *International Journal of Pharmacologic Medicine* 21 (2007): 395-404.

<sup>31</sup> Silverman WA. *Retrolental Fibroplasia. A Modern Parable*. Grune and Stratton, 1980.

<sup>32</sup> Silverman WA. A cautionary tale about supplemental oxygen: The albatross of neonatal medicine. *Pediatrics* 2004;113:394.

**From:** Walsh, Michele  
**To:** Kennedy, Kathleen A; Bell, Edward (Pediatrics); Tyson, Jon E; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS News interview  
**Date:** Friday, August 23, 2013 10:05:06 AM

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They want to interview someone to "speak on behalf of the Network" on the Day of the HHS meeting.

I responded that I was happy to speak with them on camera-  
But not on that day which is very packed.

And could only speak for myself not the Network-

If they want someone to speak on behalf of the NRN they should  
Contact NICHD Dr. Guttmacher.

I understand that they are now approaching every center's media reps.

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu  
Phone: (216) 844-3387  
Fax: (216) 844-3380

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Friday, August 23, 2013 9:25 AM  
**To:** Walsh, Michele; Bell, Edward (Pediatrics); Tyson, Jon E; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Rosemary Higgins  
**Subject:** RE: CBS News interview

Has anyone responded to this? Our media folks have now been contacted by CBS. I assume it's the same think. I was thinking that Ed has responded but now I see that Ed talked with Nature not CBS.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, August 13, 2013 12:45 PM  
**To:** Bell, Edward (Pediatrics); Tyson, Jon E; Kennedy, Kathleen A; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Rosemary Higgins  
**Subject:** RE: CBS News interview

Potentially- what program is this?

*Michele Walsh*

**Chief Division of Neonatology**

Rainbow Babies & Childrens Hospital

**Professor of Pediatrics**

Case Western Reserve University

11100 Euclid Avenue, Mailstop 6010

Cleveland, OH 44106-6010

email: [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu)

Phone: (216) 844-3387

Fax: (216) 844-3380

---

**From:** Bell, Edward (Pediatrics) [<mailto:edward-bell@uiowa.edu>]

**Sent:** Tuesday, August 13, 2013 1:12 PM

**To:** Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter

**Cc:** Wally Carlo; Rosemary Higgins

**Subject:** CBS News interview

**Importance:** High

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

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**Subject:** Re: CBS News interview  
**Date:** Friday, August 23, 2013 9:38:17 AM

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Michele has been talking with CBS. See new Public Citizen charges about TOP.

On Aug 23, 2013, at 8:25 AM, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu> wrote:

Has anyone responded to this? Our media folks have now been contacted by CBS. I assume it's the same think. I was thinking that Ed has responded but now I see that Ed talked with Nature not CBS.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, MS in Clinical Research Degree Program  
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Houston, TX 77030  
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**Cc:** Wally Carlo; Rosemary Higgins  
**Subject:** RE: CBS News interview

Potentially- what program is this?

*Michele Walsh*  
**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
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11100 Euclid Avenue, Mailstop 6010  
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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, August 22, 2013 4:37 PM  
**To:** Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: URGENT: Public Citizen: New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards

Check the e-mail I just sent you. Writing furiously as we speak.

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, August 22, 2013 4:37 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: URGENT: Public Citizen: New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards

Hi Bob:

Just checking in on this to see if you have anything; no inquiries thus far though.

Thanks,  
Renate

---

**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Thursday, August 22, 2013 2:48 PM  
**To:** Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** URGENT: Public Citizen: New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards  
**Importance:** High

Hi all:

See the Public Citizen news release below. John and I just spoke with OASPA and the goal is to (b)(5)  
(b)(5) We haven't gotten any inquiries yet but I suspect we will.

Thanks,  
Renate

---

**From:** Sye, Tait (OS/ASPA)  
**Sent:** Thursday, August 22, 2013 2:18 PM  
**To:** Burklow, John (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]  
**Cc:** Bray, John P (OS/ASPA); Baldauf, Sarah (OS/ASPA)  
**Subject:** Public Citizen: New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards

Hi-

Let's talk about this at 230.

\*\*\*

Public Citizen Press Release

<http://www.noodls.com/view/A24D4D63603AF3709BDAA87F57D8318927F70E12>

Sent: Thu, Aug 22, 2013 12:23 pm

Subject: Another unethical baby trial - government must act

**New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards**

*Lack of Information for Parents on Dire Risks to Their Premature Babies Indicates Need for Greater Oversight*

August 22, 2013

Contact: Sam Jewler (202) 588-7779; Angela Bradbery (202) 588-7741

WASHINGTON, D.C. – Just months after exposing an unethical federally funded experiment conducted on premature infants, Public Citizen has learned of another, similar trial that also poses known risks to premature babies without fully informing the parents about those risks. In a letter sent today, Public Citizen calls on Health and Human Services (HHS) Secretary Kathleen Sebelius to stop recruiting for the trial, which started only recently, and to notify parents of babies already enrolled about the risks to their children.

The National Institutes of Health-funded Transfusion of Prematures (TOP) trial is designed to determine which of two strategies for treating anemia with blood transfusions is more likely to result in death or neurologic injury in extremely premature infants who develop anemia (low blood hemoglobin, which is found in red blood cells and carries oxygen to the body). In certain respects, the ethical lapses in this trial are very similar to those in the NIH-funded Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), which Public Citizen exposed in April as subjecting premature infants to risks of blindness or death without proper consent from parents.

The TOP study apparently began in the past several months. Infants are now being enrolled at as many as 15 major academic medical centers that are part of the NIH-funded Neonatal Research Network. The infants weigh less than 2.2 pounds and are born 22 to 29 weeks into the pregnancy (any birth before 37 weeks is considered pre-term). The study is expected to involve 1,824 extremely premature infants.

In the study, half of the infants are randomly assigned to receive transfusions at a high hemoglobin level (liberal transfusion group) and half at a low hemoglobin level (restrictive transfusion group) – regardless of their individual needs. “Of note,” Public Citizen’s letter reads, “the best available evidence, previously published by some of the TOP trial investigators themselves and extensively cited in the TOP protocol, suggests, overall — as does the study’s subtitle — that the restrictive transfusion strategy is more likely to result in neurologic injury and other harms in extremely premature infants.” The letter is available at <http://www.citizen.org/hrg2150>.

Yet despite these known risks, the consent forms for the TOP trial, acquired by Public Citizen through Freedom of Information Act (FOIA) requests, have serious deficiencies resembling those found in consent forms used in the SUPPORT study. The consent forms fail to inform parents of prior research suggesting that the liberal transfusion approach has more favorable outcomes and that the purpose of the study is in fact to prove this point – which requires exposing more than 900 infants to the restrictive transfusion strategy.

Of the 17 institutional review board-approved consent forms obtained by Public Citizen, only one mentions the foreseeable risk of death or disability. Five say the research poses no risk, and 16 conflate risks of the research with risks of routine medical care. All but two of the forms fail to explain that part of the primary purpose of the research is to see which transfusion group is more likely to suffer death, and 12 fail to indicate the study’s equally primary goal of seeing which group shows more signs of neurodevelopment impairment.

“This continued pattern of egregious informed consent deficiencies in NIH-funded trials involving the most vulnerable of human beings is deeply troubling,” said Dr. Michael Carome, director of Public Citizen’s Health Research Group. “These ethical lapses may represent the tip of the iceberg.”

Public Citizen is urging Sebelius to immediately halt the TOP trial and direct HHS’ Office for Human Research Protections

**(OHRP) to open an investigation into the trial. It also is calling for OHRP to develop a plan to contact the parents of subjects already enrolled in the trial and provide them with full information about the risks, purpose and nature of the research.**

Since this is not the first such lapse in research ethics in a large multicenter trial involving premature babies, Public Citizen's letter also calls for an independent investigation of the HHS system for review and oversight of HHS-funded human subject research, and a suspension of any other similar studies currently being funded by NIH or any other HHS agency.

In the SUPPORT study, which took place from 2005-2009, 1,316 premature infants were exposed to an increased risk of blindness, brain injury and death as researchers tested two experimental approaches for managing oxygen therapy.

Publicity over the SUPPORT trial prompted HHS to announce an unusual public forum, scheduled for Wednesday, Aug. 28, from 9 a.m. to 5 p.m. at HHS headquarters in Washington, D.C. It is designed to solicit comments from experts and the public about what risks should be disclosed to participants when research is focused on the so-called "standard of care" treatment given patients for a particular condition.

Since Public Citizen publicized the lack of adequate informed consent in the SUPPORT trial, a controversy has raged in the scientific community over what kind of consent is needed in certain kinds of clinical trials. The debate goes to the heart of how research is conducted in the United States and could have far-reaching, negative implications if changes are made to weaken the ethical and regulatory standards by which trials are run.

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**To:** Myles, Renate (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Childress, Kerri (NIH/NICHD) [E]  
**Subject:** RE: URGENT: Public Citizen: New NIH-Funded Study on Premature Infants Shows Familiar Lack of Compliance With Ethical Consent Standards

Just heard from Richard Knox of NPR who wanted to know if we had any response to the public citizen letter. I told him that I just got the public citizen release about 15 minutes ago, and we were just reading it.

Richard wasn't sure if there was time for a story or not, but wanted to check to see if we had anything to say.

Dr. Higgins just had a voice mail from Dina Beasley at Reuters, which she forwarded to me about 30 seconds ago. (Haven't listened yet.)

How about if I draft a statement for OD-NICHD review?

---

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**Sent:** Thursday, August 22, 2013 2:48 PM  
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**To:** [Wally Carlo](#); [Jon Tyson](#); [Kathleen Kennedy](#); [Michele Walsh](#); [Krisa P Van Meurs \(vanmeurs@stanford.edu\)](#); [Abbot Laptook](#); [Pablo Sanchez](#); [Kristi Watterberg](#); [Brenda Poindexter](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** More on support  
**Date:** Thursday, August 22, 2013 2:49:07 PM  
**Attachments:** [Lantos on SUPPORT - ADCFNE epub 2013.pdf](#)  
[SUPPORT editorial - Nature 2013.pdf](#)

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# Learning the right lessons from the SUPPORT study controversy

John D Lantos

Ten years ago, there was well-known and widespread practice variation in the levels of oxygen that neonatologists provided to premature babies.<sup>1</sup> Neonatal intensive care units (NICUs) targeted oxygen saturations ranging from 82% to 100%. Cole and colleagues summarised the state of knowledge about oxygen therapy for premature babies: "We do not understand optimal oxygenation management in extremely low gestational age neonates (<28 weeks' gestation). No randomised controlled trial has clarified the relation between retinopathy of prematurity and blood oxygen, transcutaneous oxygen or oxygen saturation levels."<sup>2</sup> As a result, they noted, "neonatal care providers differ widely, with no consensus in their policies, practices and strong beliefs regarding oxygen management in the early and later neonatal courses of premature infants." They called for prospective randomised trials to address this crucial gap in knowledge, because "continued treatment of millions of premature infants in ignorance of what is safe and effective oxygenation is not an option."

Today, the situation is different because such studies were designed and conducted in the USA,<sup>3</sup> Canada,<sup>4</sup> Australia, New Zealand and the UK.<sup>5</sup> In the USA, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) was a National Institutes of Health (NIH)-sponsored, multicentre, prospective randomised trial of different strategies to treat lung disease in babies born at 24–27 weeks of gestation. Between 2004 and 2009, approximately 1300 infants were enrolled. The study led to a number of seminal papers that today, at long last, allow oxygen therapy to be evidence based. Babies are safer as a result.

Now, questions are being raised about whether the studies harmed the babies who participated and about whether parents were fully informed about the risks of those studies. On 7 March, the Office of Human Research Protections (OHRP) notified the researchers in SUPPORT that "...the conduct of this study was in

violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death."<sup>6</sup> A month later, the consumer advocacy organisation Public Citizen criticised the study even more harshly.<sup>7</sup> They claimed that the study should never have been done because it had been "known for decades" that higher oxygen levels cause greater retinal damage. Further, they claimed that the study entailed "real, substantial risks to...babies, some of whom subsequently may have died unnecessarily or suffered impairment of vision as a result of their participation in the study." They have now called for investigations of the consent process in other countries.<sup>8</sup> *The New York Times* weighed in with an editorial entitled 'An Ethical Breakdown' in which they called the study 'startling and deplorable.'<sup>9</sup>

The editors of *The New England Journal of Medicine* disagreed. They questioned OHRP's reasoning and conclusions. They wrote that "there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants." They concluded, "We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress."<sup>10</sup> The Director of the NIH strongly defended the study and stated that "care was never compromised for the sake of the study."<sup>11</sup>

So which is it? Was the study an egregious ethical breakdown? Or was it a model of how to make medical progress? To decide, one must look carefully at the critiques that OHRP and Public Citizen are making and evaluate whether they are valid in the light of what we knew about the study design at the outset. Today, we can also ask whether they make sense in the light of what we know about the results.

OHRP and Public Citizen claim that the consent forms were deficient. OHRP gives specific points that should have been included in the consent forms but were not:

1. The study involves substantial risks.

2. By participating in this study, the level of oxygen an infant receives would in many instances be changed from what they would have otherwise received, though it is not possible to predict what that change will be.
3. Some infants would receive more oxygen than they otherwise would have, in which case, if the researchers are correct in how they suppose oxygen affects eye development, those infants have a greater risk of going blind.
4. The level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death.

Of these, only number 2 is true. Whether or not it was adequately explained in the consent forms is less straightforward. Parents were told that conventional treatment at the time was to target oxygen saturations between 85% and 95%. This was true, based on Anderson's data. They were told that, in the study, babies would be randomised to either the higher end or the lower end of that range. That would convey to most parents that their baby was receiving different treatment than would have been given outside the trial.

Numbers 1, 2 and 4 are not true. At the time the study was conducted, the investigators did not believe that the study involved substantial risk compared to the alternative—that is, to oxygen doses determined by individual physicians based on clinical judgment. They hoped that the study might show that lower oxygen saturation targets would lead to lower rates of retinopathy without increased rates of mortality or other morbidities. They did not believe that mortality would be higher in the low oxygen group or that babies in the study would have higher mortality than babies not in the study. They should, perhaps, have explained that being in the study could increase the risk of bad outcomes, decrease that risk or have no effect at all.

Now, because we have the data, we know that the risks of bad outcomes were lower for babies in the study than babies who were not enrolled. The SUPPORT study researchers report that: "The infants in both treatment groups had lower rates of death before discharge (16.2% in the higher-oxygen-saturation group and 19.9% in the lower-oxygen-saturation group) than did those who were not enrolled (24.1%) and historical controls (23.1%), and rates of blindness did not differ between the treatment groups."<sup>12</sup>

Correspondence to Dr John D Lantos, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, Missouri 64108, USA; jlantos@cmh.edu

## Leading article

And while it was clear that some infants in the study might have received more or less oxygen than they otherwise would have, there was no evidence that they had a greater risk of going blind or of suffering brain damage or death than babies who were not in the study. That was the belief at the outset of the study and that is what the data from the study confirmed.

By OHRP's standards, doctors would have been required to exaggerate the expected risks when they sought consent. This does not meet either the spirit of informed consent or the requirements of current research regulation. Instead, this approach reflects a belief—not borne out by the data—that research is riskier than standard therapy and a moral demand that researchers communicate scientifically inaccurate information in the process of seeking parental consent.

Why would they require this? The ideas that research is risky compared to non-validated therapy and that care by protocol is inferior to care by individualised clinical judgment have been around for a long time. They used to be widely held by doctors and criticised by bioethicists as unjustifiable medical paternalism. William Silverman, a pioneer of neonatology and a staunch advocate of better clinical studies, was familiar with such arguments. He identified them as a belief in 'mystical certainty' rather than an acceptance of 'scientific uncertainty.' He noted that: "Doctors are viewed suspiciously when they ask questions—a switch from their accustomed role as providers of answers."<sup>13</sup>

What a topsy-turvy world! Today, neonatologists around the world want to carefully and collaboratively study the risks and benefits of common therapies. They publically announce their intentions and seek feedback from research review boards. Their study designs are rigorously scrutinised, and their consent forms are reviewed for accuracy and understandability. Parents are accurately informed of the reasonably foreseeable risks and benefits of the research. The studies are carefully monitored. Babies in the studies are protected from the risks of research and the risks of treatment with non-validated therapies. Their outcomes are better than those of babies not in the studies.

But then these neonatologists are criticised by advocacy groups and by the federal agencies whose mandate is to ensure the responsible conduct of research. These groups suggest that babies

would be better off if doctors would misrepresent the risks of the studies, frighten parents away, prevent responsible research and continue to treat babies based on their non-validated beliefs about what is best.

The research enterprise depends upon safety, honesty and transparency. The informed consent process is a crucial element in maintaining honesty and transparency. Consent forms should be as accurate as possible in describing the goals, methods, potential risks and potential benefits of any research. In describing risks, we must be careful to accurately compare the risks of being in a study with the risks of not being in the study. When studies involve therapies that are in widespread use, and especially when there is documentation of widespread practice variation in the use of those therapies, babies who are in studies are not at higher risk by being randomised than are the babies who are not in studies and whose treatment depends not on the study design but upon apparently random practice variation. In such situations, there may be no incremental risk to being in a study. There may even be some benefit.<sup>14 15</sup>

We should work to improve the informed consent process.<sup>16</sup> Towards that goal, we should learn from the controversy about the SUPPORT study. But we should learn the right lessons. The most important lesson to learn is that sometimes it is safer to be in a study than to not be in the study. It is sometimes better to be treated on a protocol than to have doctors make idiosyncratic clinical judgments in the absence of good evidence about risks and benefits. Honesty requires us to disclose what we know and what we don't know. Neither parents nor babies are served by a system that hides our uncertainty. And everybody is harmed by ethical standards that are exquisitely attentive to the potential risks of randomised trials but oblivious to the risks of non-validated therapies.

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**Competing interests** Children's Mercy Hospital is currently a member of the NICHD Neonatal Research Network. It was not at the time of the SUPPORT study,

and Dr Lantos was not working there at the time of the SUPPORT study.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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doi:10.1136/archdischild-2013-304916

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## Learning the right lessons from the SUPPORT study controversy

John D Lantos

*Arch Dis Child Fetal Neonatal Ed* published online August 22, 2013  
doi: 10.1136/archdischild-2013-304916

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# THIS WEEK

## EDITORIALS

**WORLD VIEW** What to do with the Russian Academy of Sciences **p.379**

**CLIMATE** Model warns of a spate of heatwaves to come **p.388**



**BONE MEAL** Marine worms devour whale skeletons **p.381**

## Subject to question

*Even when conducting clinical trials to study widely used therapies, researchers must ensure that they disclose the full risks to patients.*

Full disclosure of the potential risks to people who volunteer to be test subjects for biomedical research has been a bedrock of ethical protections for decades. Now, a fresh question has come to the fore: how best to protect human subjects in trials that examine the effectiveness of existing therapies that are already in widespread use.

On 28 August, the US office charged with protecting human research subjects will hold an unusual public meeting in Washington DC to tackle this contentious, complex issue, which has polarized the biomedical community in recent months. The Office for Human Research Protections (OHRP), part of the Department of Health and Human Services, is asking for input on how institutional ethics committees — the advisory boards that decide whether proposed trials can go ahead — should assess the risks to people in randomized studies that investigate the risks and benefits of existing treatments for the same condition. Such ‘standard of care’ trials are likely to become more widespread after being mandated in the 2010 health-care law, so a lot is riding on what the OHRP decides. It might insist that these risks be spelled out on patient-consent forms, even though patients with a particular condition would be taking one or the other medication anyway. Those who argue for looser regulations of such research say that this move could put many volunteers off, because they might mistakenly think that the research itself is adding risk of harm.

The issue has been thrust into the spotlight by a protracted controversy over a study of extremely premature infants, funded by the US National Institutes of Health. From 2005 to 2009, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) enrolled 1,316 infants born, on average, 14 weeks early and weighing less than a kilogram. Such infants struggle to breathe because of their immature lungs and so are given extra oxygen from birth. Those in the trial were assigned at random to one of two groups. In one, blood oxygen levels were kept at the higher end of the range used in US hospitals, with the attendant risk of causing an eye disorder called retinopathy of prematurity (ROP) — an abnormal growth of retinal blood vessels that blinds 400–600 US infants every year. In the other group, oxygen levels were kept at the lower end of the range, with the accompanying risks including neurodevelopmental disorders and, some experts in the field believed, death. The goal was to determine the effects of lower or higher oxygen levels on the infants’ survival, neurological development and likelihood of developing ROP. In short, the trial sought the sweet spot — the level of oxygen supplementation that would lead to maximum survival without damage.

### RISK AVERSE

In 2011 the OHRP, responding to a complaint, began to investigate the informed consent forms signed by parents at the 23 SUPPORT sites. In March this year, it concluded that the forms failed to describe “the reasonably foreseeable risks of blindness, neurological damage and death”. All but two of the forms failed to note, for instance, that

infants in the group maintained at higher oxygen levels would have a greater chance of eye damage, yet more than half said that infants in the lower-level group could benefit from a lower risk of eye disease or less need for eye surgery. None noted the increased risks of neurodevelopmental disorders in the lower-level group. None listed death as a possible risk of the procedure, although the trial protocol (not seen by parents) did list death among the related adverse events “that may be related to the study”. The consent forms did reassure parents that:

*“Transparency and respect for research subjects must be beyond reproach.”*

“Because all of the treatments proposed in this study are within standard of care, there is no predictable increase in risk for your baby.”

Much of the biomedical establishment has rallied to support the trial investigators and the ethics committees that approved the informed consent forms. They argue that the babies encountered a set of grave risks

inherent to being premature, not to being randomly assigned to one or the other arm of the trial. Because the trial administered treatment within accepted guidelines endorsed by the American Academy of Pediatrics, they say, the study added no risk and thus the consent forms were adequate.

The goals of SUPPORT were laudable and addressed a need for better information for physicians. And the study did produce illuminating findings: the infants who received lower levels (aiming to keep the oxygen saturation of their haemoglobin at 85–89%) were less likely to get severe eye disease — but more likely to die — than infants receiving oxygen at 91–95% saturation levels. But in an age in which it is more important than ever that transparency and respect for research subjects must be beyond reproach, the SUPPORT consent forms simply do not pass muster. And although it is true that, collectively, the infants enrolled in the study may have been at no greater risk of a negative outcome than infants who were not enrolled, it is not collectives who sign informed consent documents. It is individuals.

Put yourself in the position of a parent with an extremely premature infant. Would you make the decision to enrol your child in the trial if the consent form stated in simple language that babies assigned to one group were more likely to go blind, and that those in the other were at a higher risk of getting neurodevelopmental disabilities? Equally, would you decide to enrol if the form spelled out that, if you do not take part, your own physician and institution might keep your infant in the middle of the range, trying to avoid either outcome? Perhaps you might, but you would do so with full knowledge of the attendant risks. The parents in this case could not do so.

In June, under pressure from many sides, the OHRP said that it would not sanction the SUPPORT investigators and instead would hold next week’s meeting. No matter the thorniness of the issues raised there, research is still research in whatever context, and the duty to protect human subjects must remain paramount. ■

**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: OHRP and Yale  
**Date:** Wednesday, August 21, 2013 8:40:22 PM

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So, they "passed" Yale. Nature says except for two, others did not pass the muster--was Yale of one of those? Who was the other?

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
rajut@mail.nih.gov

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

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, August 21, 2013 4:03 PM  
To: Rowe, Mona (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Spong, Catherine (NIH/NICHD) [E]  
Subject: OHRP and Yale

This is available on the OHRP website -

[http://www.hhs.gov/ohrp/detrm\\_letters/YR13/jul13b.pdf](http://www.hhs.gov/ohrp/detrm_letters/YR13/jul13b.pdf)

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**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Nature Editorial (on SUPPORT): Subject to Question  
**Date:** Wednesday, August 21, 2013 8:27:53 PM

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Wah!!

**Tonse N.K. Raju, MD, DCH**

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Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Phone: 301-402-1872, Fax: 301-496-3790  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 7:16 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** Fwd: Nature Editorial (on SUPPORT): Subject to Question

FYI

Sent from my iPhone

Begin forwarded message:

**From:** "Guttmacher, Alan (NIH/NICHD) [E]" <[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)>  
**Date:** August 21, 2013, 5:22:10 PM EDT  
**To:** "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>, "Maddox, Yvonne (NIH/NICHD) [E]" <[maddoxy@exchange.nih.gov](mailto:maddoxy@exchange.nih.gov)>, "Spong, Catherine (NIH/NICHD) [E]" <[spong@c@dir49.nichd.nih.gov](mailto:spong@c@dir49.nichd.nih.gov)>  
**Subject:** FW: Nature Editorial (on SUPPORT): Subject to Question

FYI...no response to me necessary.

Alan

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**From:** Myles, Renate (NIH/OD) [E]  
**Sent:** Wednesday, August 21, 2013 4:21 PM  
**To:** Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]  
**Cc:** Devaney, Stephanie (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]  
**Subject:** Nature Editorial (on SUPPORT): Subject to Question

NATURE | EDITORIAL

Subject to question

**Even when conducting clinical trials to study widely used therapies, researchers must ensure that they disclose the full risks to patients.**

21 August 2013

Full disclosure of the potential risks to people who volunteer to be test subjects for biomedical research has been a bedrock of ethical protections for decades. Now, a fresh question has come to the fore: how best to protect human subjects in trials that examine the effectiveness of existing therapies that are already in widespread use.

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used in US hospitals, with the attendant risk of causing an eye disorder called retinopathy of prematurity (ROP) — an abnormal growth of retinal blood vessels that blinds 400–600 US infants every year. In the other group, oxygen levels were kept at the lower end of the range, with the accompanying risks including neurodevelopmental disorders and, some experts in the field believed, death. The goal was to determine the effects of lower or higher oxygen levels on the infants' survival, neurological development and likelihood of developing ROP. In short, the trial sought the sweet spot — the level of oxygen supplementation that would lead to maximum survival without damage.

### **Risk averse**

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**"Transparency and respect for research subjects must be beyond reproach."**

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Volume:

500,

Pages:

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**Date published:**

(22 August 2013)

**DOI:**

doi:10.1038/500377a

**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS news inquiry  
**Date:** Wednesday, August 21, 2013 12:49:22 PM

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I had a meeting in Bld 31, and since then have been inundated with meetings!  
Will read top to bottom in a minute.

**Tonse N.K. Raju, MD, DCH**  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 12:38 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]  
**Subject:** FW: CBS news inquiry

FYI – I had called to give you a heads up prior to the email --start from the bottom and read up – will keep you posted—  
Rose

**Rosemary D. Higgins, MD**  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 12:36 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** RE: CBS news inquiry

Hi all  
Attached is my latest word from Dr. Michele Walsh, NRN PI at Case Western Rainbow Babies – looks like she was waiting to hear back from CBS.

Rose

**Rosemary D. Higgins, MD**

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 12:07 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS news inquiry

thanks

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Bethesda, MD 20892-2425

Phone: 301-496-3454  
e-mail: [guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)  
url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 12:05 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CBS news inquiry

I just finished briefing Renate. She asked me to (b)(5)

(b)(5)

I'll keep you posted.

Thanks.

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 11:36 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: CBS news inquiry

(b)(5)

We do want our view represented, but I thought (b)(5)

(b)(5)

Alan

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, August 21, 2013 11:31 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]  
**Cc:** Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** CBS news inquiry

Hello again.

I just spoke with Kim Skeen, a producer for CBS Sunday Morning.

She would like to interview you on tape early next week for your perspective regarding OHRP's initial ruling and subsequent suspension of its findings on the Support trial.

She said that she's really interested in talking with one of the Support researchers, but wasn't having much luck in reaching someone. I explained that, although our institute was involved with the study in an advisory capacity, that it was not conducted by NIH researchers and that our role primarily involved funding for the study.

She said she understood, but still wanted to get your perspective on the events that have transpired.

If you agree, I'm thinking that the next step is for me to (b)(5)

(b)(5)

Thanks.

Bob

**From:** Das, Abhik  
**To:** Gordon Avery; gavery123@hotmail.com; huntc@nhlbi.nih.gov; mikeross@ucla.edu; kant@unc.edu; Gail, Dorothy (NIH/NHLBI) [E]; Keszler, Martin  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Christine A. Gleason  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).  
**Date:** Wednesday, August 21, 2013 10:03:53 AM  
**Attachments:** RTIdatarequest8.15.docx

---

Hello all:

You are receiving this email because in the past you have served on the DSMC for the NICHD Neonatal Research Network and reviewed interim data from the SUPPORT trial. Please see below and attached.

Thanks

**Abhik Das, Ph.D.**

**PI, Data Coordinating Center for the NICHD Neonatal Research Network**

**RTI International**

6110 Executive Blvd., Suite 902

Rockville, MD 20852-3903

e-mail: [adas@rti.org](mailto:adas@rti.org)

Phone: 301-770-8214

Fax: 301-230-4846

---

**From:** Das, Abhik  
**Sent:** Tuesday, August 20, 2013 2:23 PM  
**To:** 'Carol J. Blaisdell ([blaisdellcj@nhlbi.nih.gov](mailto:blaisdellcj@nhlbi.nih.gov))'; 'Christine A. Gleason ([cgleason@u.washington.edu](mailto:cgleason@u.washington.edu))'; 'Marian Willinger ([willingm@mail.nih.gov](mailto:willingm@mail.nih.gov))'; 'Marilee C. Allen ([mcallen@jhmi.edu](mailto:mcallen@jhmi.edu))'; 'Menachem Miodovnik'; 'Merran A. Thomson ([merran.thomson@ic.ac.uk](mailto:merran.thomson@ic.ac.uk))'; 'Michael O'Shea'; 'Robert Boyle ([RJB6J@hscmail.mcc.virginia.edu](mailto:RJB6J@hscmail.mcc.virginia.edu))'; 'Steven Weiner ([Weiner@Biostat.bsc.gwu.edu](mailto:Weiner@Biostat.bsc.gwu.edu))'; 'Traci Clemons ([tdemons@emmes.com](mailto:tdemons@emmes.com))'  
**Cc:** 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Hello All:

FYI, I received this request from the DHHS Office of Inspector General, and upon advice from NIH and RTI counsel, we will need to comply with it, and are doing so. This does include the confidential DSMC minutes for the open and closed sessions of the meetings that discussed the SUPPORT trial.

Thanks

Abhik

---

**From:** Searcy, Talisha M (OIG/OEI) [<mailto:Talisha.Searcy@oig.hhs.gov>]

**Sent:** Monday, August 19, 2013 1:36 PM

**To:** Das, Abhik

**Cc:** Yates, Kim A (OIG/OEI); Galvin, Chris P (OIG/OEI); Hereford, Russell W (OIG/OEI); Greenleaf, Joyce M (OIG/OEI)

**Subject:** Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Greetings Mr. Das,

The Office of Inspector General (OIG), Office of Evaluation and Inspections conducts national evaluations on issues of interest to Department officials, Congress, and the public. We are currently assessing the Office for Human Research Protections' (OHRP) compliance with its procedures for its evaluation of human subject protection procedures of the SUPPORT Study at the University of Alabama at Birmingham. As we discussed, NIH staff directed us to you regarding collecting necessary documentation for our review. Attached is the official document request for our study.

Please provide the requested information by **COB, Friday, August 23, 2013**. If you have any questions regarding this request, please contact me or Kim Yates at (617) 565-2911, or [Kim.Yates@oig.hhs.gov](mailto:Kim.Yates@oig.hhs.gov).

Thanks!

Talisha Searcy

**Talisha Searcy, M.P.A., M.A.**

U.S. Department of Health and Human Services

Office of Inspector General

Office of Evaluation and Inspections

330 Independence Ave. SW, Room 5650

Washington, DC 20201

Tel: (202) 619-3409

Fax: (202) 401-0556

[talisha.searcy@oig.hhs.gov](mailto:talisha.searcy@oig.hhs.gov)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

## OFFICE OF INSPECTOR GENERAL



OFFICE OF EVALUATION AND INSPECTIONS, REGION I  
JFK FEDERAL BUILDING  
ROOM 2225  
BOSTON, MA 02203

Research Triangle Institute  
PO Box 12194  
Research Triangle Park, NC 27709

RE: Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Dear Mr. Das:

The Office of Inspector General (OIG), Office of Evaluation and Inspections conducts national evaluations on issues of interest to Department officials, Congress, and the public. We are currently assessing the Office for Human Research Protections' (OHRP) compliance with its procedures for its evaluation of human subject protection procedures of the SUPPORT Study at the University of Alabama at Birmingham.

We will determine the extent to which OHRP followed its procedures and exercised its discretion in its evaluation of the SUPPORT Study. Dr. Rosemary Higgins at NIH directed us to RTI to fulfill the data request below:

### Data Request:

Please provide the following documents that relate to the SUPPORT Study:

- Copies of all Data Safety Monitoring Committee (DSMC) meeting minutes, including open and closed sessions.
  - For each closed DSMC meetings, provide, in addition to the minutes:
    - recommendations, and
    - a list of meeting attendees, if available
- All reports of adverse events that occurred in the trial at any site, and the date on which they occurred (in a spreadsheet form if you have it).

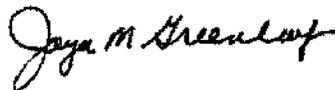
We do not need personally identifiable information (PII), so if possible, please remove it. For any PII that we receive, we will follow OIG procedures to protect all PII. Information can be submitted through an electronic file on CD or DVD or submitted in hard copy. We recommend that you use a delivery service that provides tracking. Please contact us if you wish to discuss how to submit data as securely as possible. Please provide this information no later than **8/23/2013** to the following address:

Office of Inspector General  
Office of Evaluation and Inspections  
JFK Federal Building, Room 2225  
Boston, MA 02203  
ATTN: Kim Yates

Authority for our request for information is found in the Inspector General Act of 1978 § 6, (see 5 U.S.C. App. § 2, 4, and 6)). Under the health information privacy regulation that implements HIPAA, providing the information requested in this letter is a permitted disclosure since it (a) is "required by law" to be produced to the OIG as part of your participation in a U.S. Department of Health and Human Services grant program (NIH-funded Phase III multisite clinical trials) (see 45 C.F.R. §§ 164.512(a), 164.501), and (b) will be used for "health oversight" activities by OIG, which meets the definition of a "health oversight agency" (see 45 C.F.R. §§164.512(d), 164.501).

Thank you in advance for your cooperation. If you have any questions regarding this request, please contact Kim Yates at (617) 565-2911, or [Kim.Yates@oig.hhs.gov](mailto:Kim.Yates@oig.hhs.gov).

Sincerely,



Joyce M Greenleaf  
Regional Inspector General

**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).  
**Date:** Tuesday, August 20, 2013 3:21:33 PM  
**Attachments:** [RTIdatarequest8.15.docx](#)

---

Rose, this was received.  
I sent it up our chain as an FYI also,

Carol

Carol J. Blaisdell M.D.  
Medical Officer  
Lung Development and Pediatrics  
Lung Biology and Diseases Branch  
Division of Lung Diseases  
NHLBI, NIH  
301-435-0222

---

**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Tuesday, August 20, 2013 2:23 PM  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#); [cgleason@u.washington.edu](mailto:cgleason@u.washington.edu); [Willinger, Marian \(NIH/NICHD\) \[E\]](#); [mcallen@jhmi.edu](mailto:mcallen@jhmi.edu); [Menachem Miodovnik; merran.thomson@ic.ac.uk](#); [Michael O'Shea; RJB6J@hscmail.mcc.virginia.edu](#); [Weiner@Biostat.bsc.gwu.edu](mailto:Weiner@Biostat.bsc.gwu.edu); [Traci Clemons](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Hello All:

FYI, I received this request from the DHHS Office of Inspector General, and upon advice from NIH and RTI counsel, we will need to comply with it, and are doing so. This does include the confidential DSMC minutes for the open and closed sessions of the meetings that discussed the SUPPORT trial.

Thanks

Abhik

---

**From:** [Searcy, Talisha M \(OIG/OEI\) \[mailto:Talisha.Searcy@oig.hhs.gov\]](#)  
**Sent:** Monday, August 19, 2013 1:36 PM  
**To:** Das, Abhik  
**Cc:** [Yates, Kim A \(OIG/OEI\)](#); [Galvin, Chris P \(OIG/OEI\)](#); [Hereford, Russell W \(OIG/OEI\)](#); [Greenleaf, Joyce M \(OIG/OEI\)](#)  
**Subject:** Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Greetings Mr. Das,

The Office of Inspector General (OIG), Office of Evaluation and Inspections conducts national evaluations on issues of interest to Department officials, Congress, and the public. We are currently assessing the Office for Human Research Protections' (OHRP) compliance with its procedures for its evaluation of human subject protection procedures of the SUPPORT Study at the University of Alabama at Birmingham. As we discussed, NIH staff directed us to you regarding collecting necessary documentation for our review. Attached is the official document request for our study.

Please provide the requested information by **COB, Friday, August 23, 2013**. If you have any questions regarding this request, please contact me or Kim Yates at (617) 565-2911, or [Kim.Yates@oig.hhs.gov](mailto:Kim.Yates@oig.hhs.gov).

Thanks!

Talisha Searcy

**Talisha Searcy, M.P.A., M.A.**

U.S. Department of Health and Human Services

Office of Inspector General

Office of Evaluation and Inspections

330 Independence Ave. SW, Room 5650

Washington, DC 20201

Tel: (202) 619-3409

Fax: (202) 401-0556

[talisha.searcy@oig.hhs.gov](mailto:talisha.searcy@oig.hhs.gov)

**From:** Das, Abhik  
**To:** richard.ehrenkranz@vale.edu; nfiner@ucsd.edu; SDuara@med.miami.edu; Ivan.Frantz@childrens.harvard.edu; Roger Faix; McGowan, Elisabeth C  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).  
**Date:** Tuesday, August 20, 2013 2:27:40 PM  
**Attachments:** RTIdatarequest8.15.docx

---

Hello all:

I inadvertently missed adding you to the email below.

My apologies!

Thanks

Abhik

---

**From:** Das, Abhik  
**Sent:** Tuesday, August 20, 2013 2:19 PM  
**To:** '[SCRN] Stoll, Barbara (barbara\_stoll@oz.ped.emory.edu)'; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Anne Marie Reynolds'; 'Barbara Schmidt'; 'Bell, Edward'; 'Bill Truog'; 'Brenda Poindexter (bpoindex@iu.edu)'; 'Carl D'Angio'; 'Das, Abhik (adas@rti.org)'; 'Gantz, Marie (mgantz@rti.org)'; 'goldb008@mc.duke.edu'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'kwatterberg@salud.unm.edu'; 'Leif Nelin'; 'mcw3@cwru.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'RAP32@columbia.edu'; 'Satyan Lakshminrusimha'; 'sshankar@med.wayne.edu'; 'Uday Devaskar'; 'vanmeurs@leland.stanford.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'  
**Subject:** FW: Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Hello All:

I received this request from the DHHS Office of Inspector General, and upon advice from NIH and RTI counsel, we will need to comply with it, and are doing so. This does NOT entail any release of SUPPORT data beyond DHHS, and we will only provide de-identified data to the IG office.

Thanks

Abhik

---

**From:** Searcy, Talisha M (OIG/OEI) [mailto:Talisha.Searcy@oig.hhs.gov]  
**Sent:** Monday, August 19, 2013 1:36 PM  
**To:** Das, Abhik  
**Cc:** Yates, Kim A (OIG/OEI); Galvin, Chris P (OIG/OEI); Hereford, Russell W (OIG/OEI); Greenleaf, Joyce M (OIG/OEI)  
**Subject:** Documentation Request for Office of Inspector General Review of Office for Human Research Protections' Evaluation of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

Greetings Mr. Das,

The Office of Inspector General (OIG), Office of Evaluation and Inspections conducts national evaluations on issues of interest to Department officials, Congress, and the public. We are currently assessing the Office for Human Research Protections' (OHRP) compliance with its procedures for its evaluation of human subject protection procedures of the SUPPORT Study at the University of Alabama at Birmingham. As we discussed, NIH staff directed us to you regarding collecting necessary documentation for our review. Attached is the official document request for our study.

Please provide the requested information by **COB, Friday, August 23, 2013**. If you have any questions regarding this request, please contact me or Kim Yates at (617) 565-2911, or [Kim.Yates@oig.hhs.gov](mailto:Kim.Yates@oig.hhs.gov).

Thanks!

Talisha Searcy

**Talisha Searcy, M.P.A., M.A.**

U.S. Department of Health and Human Services

Office of Inspector General

Office of Evaluation and Inspections

330 Independence Ave. SW, Room 5650

Washington, DC 20201

Tel: (202) 619-3409

Fax: (202) 401-0556

[talisha.searcy@oig.hhs.gov](mailto:talisha.searcy@oig.hhs.gov)

**From:** Tyson, Jon E  
**To:** Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Bell, Edward (Pediatrics); Kennedy, Kathleen A; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Interview  
**Date:** Monday, August 19, 2013 7:18:30 PM

---

Yes, I have 7 minutes to speak.

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Monday, August 19, 2013 6:16 PM  
**To:** Poindexter, Brenda B; Wally Carlo, M.D.; Bell, Edward (Pediatrics); Tyson, Jon E; Kennedy, Kathleen A; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Rosemary Higgins  
**Subject:** RE: Interview

Thanks Ed! I am sure that you were excellent as always.  
I am waiting to hear back from the CBS news group who want  
An on camera interview on Aug 28 in Washington DC.  
Will keep all posted.  
PS: I was selected to speak at Aug 28 meeting- will circulate slides  
Methods of Defining Risk in CER.  
Has anyone else heard?

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu  
Phone: (216) 844-3387  
Fax: (216) 844-3380

---

**From:** Poindexter, Brenda B [mailto:bpoindex@iu.edu]  
**Sent:** Monday, August 19, 2013 6:47 PM  
**To:** Wally Carlo, M.D.; Bell, Edward (Pediatrics); Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Rosemary Higgins  
**Subject:** Re: Interview

Echo that – thanks so much. I'm sure you were an excellent spokesperson!  
Brenda

---

**From:** "<Wally Carlo>", Wally Carlo <wcarlo@peds.uab.edu>  
**Date:** Monday, August 19, 2013 5:28 PM  
**To:** Ed Bell <Edward-bell@uiowa.edu>, Jon E Tyson <Jon.E.Tyson@uth.tmc.edu>, Kathleen Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>, Michele Walsh <mcw3@cwru.edu>, Krisa VanMeurs <vanmeurs@stanford.edu>, "alaptook@WIHRI.org" <alaptook@WIHRI.org>, Pablo

Sanchez <[Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu)>, Kristi Watterberg  
<[KWatterberg@salud.unm.edu](mailto:KWatterberg@salud.unm.edu)>, Brenda Poindexter <[bpoindex@iupui.edu](mailto:bpoindex@iupui.edu)>  
Cc: Rosemary Higgins <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
Subject: Re: Interview

Ed.

Thx so much.

Wally

-----Original message-----

From: "Bell, Edward (Pediatrics)" <[edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)>  
To: "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>, Jon Tyson <[Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu)>, Kathleen Kennedy <[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)>, Michele Walsh <[mcw3@cwru.edu](mailto:mcw3@cwru.edu)>, "Krisa P Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu))" <[vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)>, Abbot Laptook <[ALaptook@wihri.org](mailto:ALaptook@wihri.org)>, Pablo Sanchez <[Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu)>, Kristi Watterberg <[kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)>, Brenda Poindexter <[bpoindex@iupui.edu](mailto:bpoindex@iupui.edu)>  
Cc: Rosemary Higgins <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
Sent: Mon, Aug 19, 2013 21:16:57 GMT+00:00  
Subject: Interview

I did a phone interview today with a journalist who is writing a story about the SUPPORT controversy for Nature. She reached me through the AAP. We talked for nearly an hour. She asked good questions. I hope the story is OK and she ignores anything stupid I said and quotes only the parts I would choose.

---

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---

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

by law.

**From:** [Kristi Watterberg](#)  
**To:** [Michele Walsh](#); [Brenda Poindexter](#); [Wally Carlo](#); [Krisa P Van Meurs \(vanmeurs@stanford.edu\)](#); [Edward \(Pediatrics\) Bell](#); [Jon Tyson](#); [Kathleen Kennedy](#); [Pablo Sanchez](#); [Abbot Laptook](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: Interview  
**Date:** Monday, August 19, 2013 5:49:42 PM

---

Thanks for all the heavy lifting you're doing with the media, Ed - you've done a fantastic job!

Kristi

>>> "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> 8/19/2013 3:16 PM >>>

I did a phone interview today with a journalist who is writing a story about the SUPPORT controversy for Nature. She reached me through the AAP. We talked for nearly an hour. She asked good questions. I hope the story is OK and she ignores anything stupid I said and quotes only the parts I would choose.

---

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---

**From:** [Bell, Edward \(Pediatrics\)](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Interview  
**Date:** Monday, August 19, 2013 5:38:12 PM

---

Yes

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, August 19, 2013 4:37 PM  
**To:** Bell, Edward (Pediatrics)  
**Subject:** Re: Interview

Ed

Did you speak with Meredith Wadman?

Thanks

Rose

Sent from my iPhone

On Aug 19, 2013, at 5:16 PM, "Bell, Edward (Pediatrics)" <[edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)<<mailto:edward-bell@uiowa.edu>>> wrote:

I did a phone interview today with a journalist who is writing a story about the SUPPORT controversy for Nature. She reached me through the AAP. We talked for nearly an hour. She asked good questions. I hope the story is OK and she ignores anything stupid I said and quotes only the parts I would choose.

---

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---

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---

**From:** Tyson, Jon E  
**To:** Bell, Edward (Pediatrics); Wally Carlo; Kennedy, Kathleen A; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Lantook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Interview  
**Date:** Monday, August 19, 2013 5:21:17 PM

---

Thanks, Ed, for doing this at (b)(6). I'll bet that as usual you did a great job (and better, I'm sure, than I could have done).

**From:** Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]  
**Sent:** Monday, August 19, 2013 4:17 PM  
**To:** Wally Carlo; Tyson, Jon E; Kennedy, Kathleen A; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Lantook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Rosemary Higgins  
**Subject:** Interview

I did a phone interview today with a journalist who is writing a story about the SUPPORT controversy for Nature. She reached me through the AAP. We talked for nearly an hour. She asked good questions. I hope the story is OK and she ignores anything stupid I said and quotes only the parts I would choose.

---

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---

**From:** Kristi Watterberg  
**To:** [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)  
**Cc:** [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [bpointex@iupui.edu](mailto:bpointex@iupui.edu); Higgins, Rosemary (NIH/NICHD) [E]; [WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu); [vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu); [Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [ALaptook@whri.org](mailto:ALaptook@whri.org)  
**Subject:** Re: CBS News interview  
**Date:** Wednesday, August 14, 2013 10:26:05 AM

---

(b)(6) so I'm not making any commitments this month til after that. Kristi

Sent from my iPhone

On Aug 13, 2013, at 11:11 AM, "Bell, Edward (Pediatrics)" <[edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)> wrote:

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

---

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---

**From:** Bell, Edward (Pediatrics)  
**To:** Walsh, Michele; Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Higgins, Rosemary (NIH/NICHD) [F]  
**Subject:** RE: CBS News interview  
**Date:** Tuesday, August 13, 2013 1:46:52 PM

---

I didn't ask. Maybe CBS Evening News or 60 Minutes?

---

**From:** Walsh, Michele [mailto:Michele.Walsh@uhhospitals.org]  
**Sent:** Tuesday, August 13, 2013 12:45 PM  
**To:** Bell, Edward (Pediatrics); Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Rosemary Higgins  
**Subject:** RE: CBS News interview

Potentially- what program is this?

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu)  
Phone: (216) 844-3387  
Fax: (216) 844-3380

---

**From:** Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]  
**Sent:** Tuesday, August 13, 2013 1:12 PM  
**To:** Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Rosemary Higgins  
**Subject:** CBS News interview  
**Importance:** High

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

---

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

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---

**From:** Wally Carlo, M.D.  
**To:** Bell, Edward (Pediatrics); Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs (vanmeurs@stanford.edu); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: CBS News interview  
**Date:** Tuesday, August 13, 2013 1:14:08 PM

Because of the (b)(6)

(b)(6)

Wally

-----Original message-----

**From:** "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu>  
**To:** Jon Tyson <Jon.E.Tyson@uth.tmc.edu>, Kathleen Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>, Michele Walsh <mcw3@cwru.edu>, "Krisa P Van Meurs (vanmeurs@stanford.edu)" <vanmeurs@stanford.edu>, Abbot Laptook <ALaptook@wihri.org>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>, Kristi Watterberg <kwatterberg@salud.unm.edu>, Brenda Poindexter <bpoindex@iupui.edu>  
**Cc:** "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, Rosemary Higgins <higginsr@mail.nih.gov>  
**Sent:** Tue, Aug 13, 2013 17:11:33 GMT+00:00  
**Subject:** CBS News interview

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

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**From:** [Raju, Tonse \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CBS News interview  
**Date:** Tuesday, August 13, 2013 1:14:37 PM

---

Do you think it is the *60 Minutes*?

Tonse N.K. Raju, MD, DCH  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Childhealth and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
rajut@mail.nih.gov

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

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, August 13, 2013 1:12 PM  
To: Raju, Tonse (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
Subject: FW: CBS News interview  
Importance: High

Hi

I was cc'd so do not (b)(5)

Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

Pregnancy and Perinatology Branch

NIH

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

From: Bell, Edward (Pediatrics) [<mailto:edward-bell@uiowa.edu>]  
Sent: Tuesday, August 13, 2013 1:12 PM  
To: Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu));  
Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
Cc: Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: CBS News interview  
Importance: High

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

---

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---

**From:** Raju, Tonse (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** RE: CBS News interview  
**Date:** Tuesday, August 13, 2013 1:13:29 PM

---

Agree.

**Tonse N.K. Raju, MD, DCH**

Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Childhealth and Human Development  
National Institutes of Health  
Phone: 301-402-1872, Fax: 301-496-3790  
[rajut@mail.nih.gov](mailto:rajut@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, August 13, 2013 1:12 PM  
**To:** Raju, Tonse (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Subject:** FW: CBS News interview  
**Importance:** High

Hi

I was cc'd so do not (b)(5)

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bell, Edward (Pediatrics) [<mailto:edward-bell@uiowa.edu>]  
**Sent:** Tuesday, August 13, 2013 1:12 PM  
**To:** Jon Tyson; Kathleen Kennedy; Michele Walsh; Krisa P Van Meurs ([vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu)); Abbot Laptook; Pablo Sanchez; Kristi Watterberg; Brenda Poindexter  
**Cc:** Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** CBS News interview  
**Importance:** High

Would one of you be willing to be interviewed on camera by Kim Skeen of CBS News about the SUPPORT controversy? UAB referred the reporter to me, and I am pushing hard to prepare for a conference I will attend starting tomorrow. I think it is important for someone

to represent us, as I don't think it would be good if the reporter said that none of the investigators was willing to be interviewed. I have Kim's contact information.

Ed

---

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---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: NRN SUPPORT publications  
**Date:** Tuesday, August 13, 2013 8:48:27 AM

We could make the (b)(5)

(b)(5)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, August 13, 2013 8:47 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: NRN SUPPORT publications

Maybe we need to (b)(5)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, August 13, 2013 8:46 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: NRN SUPPORT publications

Dammit. Don't know how the (b)(6) address got in there. I recalled it and sent it again to the others. I got a message back from Dorothy's email with contact info for people at NHLBI in it. Will try to call them to see if they have a way to contact her.

I am literally drowning in detailed minutiae with these acknowledgement agreements!

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, August 13, 2013 8:18 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: NRN SUPPORT publications

Stephanie-

This is not the correct (b)(6) and who is (b)(6)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, August 13, 2013 8:12 AM  
**To:** Berberich, Mary (NIAID); Blaize, Onica (CDC/OPHPR/DSLRL); Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]; Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** NRN SUPPORT publications

We have several papers coming out soon based on data from the SUPPORT trial. Attached is the first one from Dr. Ambalavanan.

He is planning on submitting it to the journal Pediatrics, which now has a policy that the authors must have written approval from everyone in the Acknowledgements to be listed there. We have traditionally included NIH personnel in the NRN Acknowledgement lists. If you would like to be listed, please complete the agreement below and return it to me.

Thank you,

Stephanie

---

Stephanie Wilson Archer  
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

---

**ACKNOWLEDGEMENT AGREEMENT**

My full name and degree(s) (as it should appear in print):	
---	--

I worked on the Neonatal Research Network at this Center:	
From this date:	
To this date:	

**Check which applies:**

I agree to be included in the Acknowledgements sections of manuscripts using data from the studies and trials conducted during the time I worked on the NRN – including main study papers and all relevant secondary and ancillary papers.

I do not wish to be included in Acknowledgements sections for the NICHD Neonatal Research Network.

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Gail, Dorothy (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]; Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** NRN SUPPORT publications  
**Date:** Tuesday, August 13, 2013 8:42:23 AM  
**Attachments:** Ambal. Association of PaCO2 with outcomes in SUPPORT. 2013-08-01.docx

---

We have several papers coming out soon based on data from the SUPPORT trial. Attached is the first one from Dr. Ambalavanan.

He is planning on submitting it to the journal Pediatrics, which now has a policy that the authors must have written approval from everyone in the Acknowledgements to be listed there. We have traditionally included NIH personnel in the NRN Acknowledgement lists. If you would like to be listed, please complete the agreement below and return it to me.

Thank you,

Stephanie

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

---

#### ACKNOWLEDGEMENT AGREEMENT

My full name and degree(s) (as it should appear in print):	
I worked on the Neonatal Research Network at this Center:	
From this date:	
To this date:	

**Check which applies:**

- I agree to be included in the Acknowledgements sections of manuscripts using data from the studies and trials conducted during the time I worked on the NRN – including main study papers and all relevant secondary and ancillary papers.
-

I do not wish to be included in Acknowledgements sections for the NICHD Neonatal  
\_\_\_\_\_ Research Network.

**Title:**

**Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

**Authors:**

Namasivayam Ambalavanan MD<sup>1</sup>; Waldemar A. Carlo MD<sup>1</sup>; Lisa A. Wrage MPH<sup>2</sup>; Abhik Das PhD<sup>3</sup>; Matthew Laughon MD MPH<sup>4</sup>; C. Michael Cotten MD MHS<sup>5</sup>; Kathleen A. Kennedy MD MPH<sup>6</sup>; Abbot R. Laptook MD<sup>7</sup>; Seetha Shankaran MD<sup>8</sup>; Michele C. Walsh MD MS<sup>9</sup>; Rosemary D. Higgins MD<sup>10</sup>; For the SUPPORT Study Group of the NICHD Neonatal Research Network

**Author Affiliations:**

<sup>1</sup>Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; <sup>2</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD; <sup>4</sup>Department of Pediatrics, University of North Carolina, Chapel Hill, NC; <sup>5</sup>Department of Pediatrics, Duke University, Durham, NC; <sup>6</sup>Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; <sup>7</sup>Department of Pediatrics, Women and Infants Hospital, Providence, RI; <sup>8</sup>Department of Pediatrics, Wayne State University, Detroit, MI; <sup>9</sup>Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; <sup>10</sup>*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

**Short Title: PaCO<sub>2</sub> and IVH**

**Abbreviations:** BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

**Keywords:** Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

**Corresponding author/Reprint requests:**

Namasivayam Ambalavanan, MD  
176F Suite 9380, Women and Infants Center, 619 South 20<sup>th</sup> St.,  
University of Alabama at Birmingham, Birmingham, AL 35249  
Tel (205) 934-4680 Fax (205) 934-3100 Email: ambal@uab.edu

**Funding source:** Supported by grants from the National Institute of Child Health and Human Development and the Department of Health and Human Services with co-funding from the National Heart, Lung, and Blood Institute (NHLBI) (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27871, U10 HD27880, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, U10 HD53124) and from the National Institutes of Health (M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, M01 RR125, M01 RR633,

M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

**Conflicts of interest:** The authors have no conflicts of interest relevant to this article to disclose.

**Word count:** abstract: 250; text of manuscript: 3075 (Introduction, Methods, Results, and Discussion).

**What's known on this subject:** Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

**What this study adds:** Higher  $\text{PaCO}_2$  and greater fluctuation in  $\text{PaCO}_2$  were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of  $\text{PaCO}_2$  with  $\text{FiO}_2$  and days of ventilation support higher maximum  $\text{PaCO}_2$  as a marker of illness severity in extremely premature infants

**ABSTRACT:**

**Objective:** To determine the association of PaCO<sub>2</sub> with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO<sub>2</sub> targets of 85-89% vs 91-95%) and ventilation strategies. Five PaCO<sub>2</sub> variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO<sub>2</sub>], hypocapnic [lowest quartile of Min PaCO<sub>2</sub>], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO<sub>2</sub>]). Adjusted and unadjusted analyses compared PaCO<sub>2</sub> variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all p <0.0001). A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> (r<sub>s</sub>0.55, p<0.0001) & ventilator days (r<sub>s</sub>0.61, p<0.0001). **Conclusions:** Higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). Correlation of PaCO<sub>2</sub> with FiO<sub>2</sub> and ventilator days supports higher Max PaCO<sub>2</sub> as a marker of illness severity.

(Abstract Word Count = 250)

## MANUSCRIPT TEXT

### INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)<sup>1</sup>, periventricular leukomalacia (PVL)<sup>2, 3</sup>, bronchopulmonary dysplasia (BPD)<sup>4</sup>, and subsequent neurodevelopmental impairment (NDI)<sup>5</sup>. Increased  $\text{PaCO}_2$  increases cerebral blood flow,<sup>6-8</sup> while decreased  $\text{PaCO}_2$  reduces cerebral blood flow and electrical activity, while increasing cerebral fractional oxygen extraction.<sup>9</sup> We have previously shown that both high and low  $\text{PaCO}_2$  levels and wide fluctuations in  $\text{PaCO}_2$  are associated with a higher risk of severe IVH (sIVH; IVH Grades III or IV).<sup>1</sup> Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.<sup>2, 3, 10</sup>

Cerebral blood flow decreases slightly with increased oxygenation<sup>8</sup> but the interactions between  $\text{PaCO}_2$  and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher  $\text{PaCO}_2$ <sup>4, 11, 12</sup> as well as a lower oxygen saturation ( $\text{SpO}_2$ ) target,<sup>13</sup> permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher  $\text{PaCO}_2$  (permissive hypercapnia) as well as a lower  $\text{PaO}_2$  (targeting a lower  $\text{SpO}_2$  range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation and compared outcomes in infants randomly assigned to  $\text{SpO}_2$  targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a  $\text{PaCO}_2 > 65$  mm Hg permitted intubation, while a  $\text{PaCO}_2 < 65$  mm Hg with a  $\text{pH} > 7.20$  was a mandatory extubation criterion) or intubation and surfactant within 1 hour after birth (a

PaCO<sub>2</sub><50 mm Hg with a pH>7.30 was a mandatory extubation criterion).<sup>13, 14</sup> Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP (higher PaCO<sub>2</sub> target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by postnatal day 7. In the lower SpO<sub>2</sub> target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes although a trend for reduced BPD (physiological definition)<sup>15, 16</sup> was noted in the lower SpO<sub>2</sub> target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).<sup>13</sup> However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups.<sup>17</sup>

It is possible that clinical outcomes that are not significantly different by SpO<sub>2</sub> target groups might be different when the combination of PaCO<sub>2</sub> and SpO<sub>2</sub> is analyzed. We hypothesized that both extremes of PaCO<sub>2</sub> would be associated with severe IVH, and that effect modification of SpO<sub>2</sub> will be observed, with hypercapnia associated with sIVH in the low but not high SpO<sub>2</sub> group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO<sub>2</sub>, and that higher PaCO<sub>2</sub> will be associated with a higher risk of NDI.

## **PATIENTS AND METHODS**

### **Patient characteristics:**

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.<sup>13, 14</sup> Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical

outcomes, and treatment. The characteristics of this population<sup>13</sup> and of the follow-up cohort<sup>17</sup> have been previously reported.

### **PaCO<sub>2</sub> variables**

Five PaCO<sub>2</sub> variables were defined for this observational study, using routine blood gas measurements not governed by study protocol. Data were collected on all PaCO<sub>2</sub> from blood gases done at 3 daily time points closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max PaCO<sub>2</sub>), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO<sub>2</sub> was calculated as described previously:<sup>1</sup> briefly, the sum of all PaCO<sub>2</sub> values multiplied by the corresponding time interval (from previous blood gas) was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5<sup>th</sup>-95<sup>th</sup> centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO<sub>2</sub> over days 1-14 into quartiles. Infants with minimum PaCO<sub>2</sub> in the lowest quartile who were not also in the highest quartile of maximum PaCO<sub>2</sub> were then categorized as 'hypocapnic'. Infants with maximum PaCO<sub>2</sub> levels in the highest quartile who were not also in the lowest quartile of minimum PaCO<sub>2</sub> level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO<sub>2</sub> and the highest quartile of maximum PaCO<sub>2</sub> were categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO<sub>2</sub> level fall in quartiles 2-4 and maximum PaCO<sub>2</sub> levels fall in quartiles 1-3 were categorized as 'normocapnic'.

### **Other variables**

Maternal hypertension was defined as pregnancy induced hypertension (PIH). Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum  $\text{FiO}_2$  was defined as the maximum of  $\text{FiO}_2$  at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as  $\text{FiO}_2 > 0.4$  and mechanical ventilation for 8+ hours in the 1<sup>st</sup> 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),<sup>18</sup> and BPD was defined using the physiologic definition at 36 w PMA.<sup>15, 16</sup> Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.<sup>17</sup>

### Statistical Analysis

The  $\text{PaCO}_2$  and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the  $\text{PaCO}_2$  and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ( $p < .05$ ) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis-generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the maximum  $\text{PaCO}_2$ , the 4 level  $\text{PaCO}_2$  categorical variable, as well as time-weighted  $\text{PaCO}_2$  were obtained using generalized estimating equation (GEE) models for binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same

treatment arm in SUPPORT. Variables included in models along with the PaCO<sub>2</sub> variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes, and center. SUPPORT treatment group variables (High/Low SpO<sub>2</sub>; CPAP/ventilator) were also included in models that contained maximum PaCO<sub>2</sub> and the 4 level PaCO<sub>2</sub> variable. Interactions of these PaCO<sub>2</sub> and treatment group variables were also included to assess if the effect of PaCO<sub>2</sub> varied by treatment group. A variable for actual median SpO<sub>2</sub> in the first 14 days was included in the model that contained time-weighted PaCO<sub>2</sub>. The interaction of these two variables was included to assess if the effect of time-weighted PaCO<sub>2</sub> varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

## RESULTS

Adjusted analysis for Severe IVH/Death (**Table 1**):

Maximum PaCO<sub>2</sub> was significantly associated with higher odds of sIVH/death (OR 1.39, 95% CI 1.27-1.53 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ). No interaction was found between PaCO<sub>2</sub> category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (High or Low SpO<sub>2</sub>), but the interaction term for time-weighted PaCO<sub>2</sub> and median SpO<sub>2</sub> in the first 14 days was significant ( $p < 0.05$ ), with a higher OR associated with a lower median SpO<sub>2</sub> (OR of 1.6 for median SpO<sub>2</sub> of 91, 1.44 for SpO<sub>2</sub> of 92, 1.30 for SpO<sub>2</sub> of 93, 1.18 for SpO<sub>2</sub> of 94) indicating that a higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

Other variables associated ( $p < 0.05$ ) with sIVH/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for BPD/Death (**Table 2**):

Maximum PaCO<sub>2</sub> (OR 1.57, 95% CI 1.41-1.75 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 2.41, 95% CI 1.89-3.09 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of BPD/death. The interaction term between PaCO<sub>2</sub> category and treatment group (High or Low SpO<sub>2</sub>) was significant for fluctuators ( $p=0.006$ ), with the OR for fluctuators in the High SpO<sub>2</sub> group being 7.4, as compared to 1.18 for the low SpO<sub>2</sub> group.

Other variables associated ( $p < 0.05$ ) with BPD/death included: lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (**Table 3**):

Maximum PaCO<sub>2</sub> (OR 1.38, 95% CI 1.25-1.52 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 1.44, 95% CI 1.09-1.90 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of NDI/death. No significant interactions were noted between PaCO<sub>2</sub> category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (reference group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with NDI/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for Death before discharge (**Table 4**):

Maximum PaCO<sub>2</sub> (OR 1.36, 95% CI 1.22-1.51 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) was associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (reference

group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with death before discharge included: lower birth weight, male gender, absence of PIH, and center.

As higher maximum  $\text{PaCO}_2$  may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum  $\text{FiO}_2$ , days of mechanical ventilation, and severe illness), correlations of maximum  $\text{PaCO}_2$  with maximum  $\text{FiO}_2$ , days of ventilation, and severe illness (as previously defined) were calculated. Maximum  $\text{PaCO}_2$  was positively correlated with both maximum  $\text{FiO}_2$  (Spearman correlation coefficient = 0.55,  $p < 0.0001$ ) and days of ventilation (Spearman correlation coefficient = 0.61,  $p < 0.0001$ ). There was also a significant difference in  $\text{PaCO}_2$  level by infants defined as having severe illness (median maximum  $\text{PaCO}_2 = 78$ ) vs. infants having no severe illness (median maximum  $\text{PaCO}_2 = 61$ ),  $p < 0.0001$ .

#### Unadjusted Results (Supplemental Tables 1-4):

All  $\text{PaCO}_2$  variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in  $\text{PaCO}_2$  as compared to those without sIVH. Maximum  $\text{PaCO}_2$  demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum  $\text{PaCO}_2$  between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted  $\text{PaCO}_2$  were statistically highly significant ( $p < 0.0001$ ) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted

PaCO<sub>2</sub> compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

## DISCUSSION

We found that extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO<sub>2</sub> in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO<sub>2</sub>, days of ventilation, and severe illness). A higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> and not in the low SpO<sub>2</sub> group.

Our study has the limitation that infants in the SUPPORT trial<sup>13, 14</sup> were not primarily randomized to different specific PaCO<sub>2</sub> ranges as in the randomized trials of permissive hypercapnia<sup>4, 12, 19</sup> but to interventions (Early CPAP vs. intubation/surfactant) with different PaCO<sub>2</sub> goals. Data on corresponding ventilator settings and oxygenation index are not available to determine if reduction of PaCO<sub>2</sub> using higher ventilator settings was associated with better outcome in the SUPPORT trial. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Eighteen to 22 month follow-up was achieved in most infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups, probably because randomization in this trial most likely led to a similar range of PaCO<sub>2</sub> in both SpO<sub>2</sub> groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in

PaCO<sub>2</sub> secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.<sup>14</sup> An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (high or low SpO<sub>2</sub> target), in order to distinguish illness severity and effects of treatment group allocation (e.g. higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO<sub>2</sub> levels and wide fluctuations in PaCO<sub>2</sub> are associated with an increased risk of sIVH.<sup>1</sup> The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO<sub>2</sub> were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO<sub>2</sub>. As maximum PaCO<sub>2</sub> was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO<sub>2</sub> had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average PaCO<sub>2</sub> in combination with a lower SpO<sub>2</sub> being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) PaCO<sub>2</sub> even in infants without severe IVH was  $\geq 48$  mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the “permissive hypercapnia” range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.<sup>12</sup> Our data indicate clinical practices in academic centers have evolved to maintain PaCO<sub>2</sub> in the permissive hypercapnia

range. However, as the maximum PaCO<sub>2</sub> exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO<sub>2</sub> within this narrow range is difficult.

A higher maximum and time-weighted PaCO<sub>2</sub> and a greater magnitude of fluctuation in PaCO<sub>2</sub> were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher PaCO<sub>2</sub> rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO<sub>2</sub> elimination for a given minute ventilation, due to a higher alveolar CO<sub>2</sub> (P<sub>A</sub>CO<sub>2</sub>). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing PaCO<sub>2</sub>, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.<sup>4, 11, 12, 19</sup> In the largest randomized trial of permissive hypercapnia to date, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group (p<0.01).<sup>4</sup> An interesting finding in the present study was that greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> but not in the low SpO<sub>2</sub> group. It is speculated that higher oxygen exposure in the high SpO<sub>2</sub> group may interact with volutrauma/atelectrauma associated with fluctuating PaCO<sub>2</sub> possibly increasing the risk for BPD/death.

Maximum PaCO<sub>2</sub> was also significantly associated with higher NDI/death, confirming our previous single-center study.<sup>5</sup> This association may be secondary to maximum PaCO<sub>2</sub> being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.<sup>20</sup> Alterations in PaCO<sub>2</sub> may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO<sub>2</sub><sup>6-8</sup> may result in sIVH<sup>1</sup> and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO<sub>2</sub><sup>9</sup> may lower white matter perfusion and result in periventricular leukomalacia (PVL).<sup>2, 3, 10</sup> Brain injury associated with extremes of PaCO<sub>2</sub> may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.<sup>21, 22</sup>

In conclusion, our work demonstrates that maximum PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, maximum PaCO<sub>2</sub> may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.

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University of Iowa Children's Hospital (U10 HD53109, UL1 TR442, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Michael J. Acarregui, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Janell Fuller, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary J. Myers, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augustino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Roy J. Heyne, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN;

Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia W. Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Roger G. Faix, MD; Bradley A. Yoder, MD; Anna Bodnar, MD; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Athina Pappas, MD; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, U11 TR142, M01 RR125) – Richard A. Ehrenkranz, MD; Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The

George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

**Table 1: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of severe IVH/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.39 (1.27-1.53)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.11 (0.73-1.67)	0.63
<b>Hypercapnic</b>	2.60 (1.77-3.82)	<0.0001
<b>Fluctuator</b>	2.81 (1.68-4.72)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub>**</b> <b>(per 10 mm Hg)</b>		
<b>Median SpO<sub>2</sub>=91</b>	1.60 (1.17-2.17)	0.003
<b>Median SpO<sub>2</sub>=94</b>	1.18 (0.85-1.62)	0.32

\*\* interaction term for time-weighted PaCO<sub>2</sub> x Median SpO<sub>2</sub> in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted PaCO<sub>2</sub> depended on level of Median SpO<sub>2</sub>.

**Table 2:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of BPD/death

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.57 (1.41-1.75)	<0.0001
<b>PaCO<sub>2</sub> Category: <u>High SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	0.73 (0.46-1.16)	0.18
<b>Hypercapnic</b>	2.54 (1.41-4.60)	0.002
<b>Fluctuator</b>	7.4 (2.6-21.0)	0.0002
<b>Normocapnic</b>	REFERENCE	-
<b><u>Low SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	1.01 (0.63-1.63)	0.96
<b>Hypercapnic</b>	3.38 (1.93-5.93)	<0.0001
<b>Fluctuator</b>	1.18 (0.51-2.70)	0.70
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	2.41 (1.89-3.09)	<0.0001

\*\* interaction term for PaCO<sub>2</sub> category x treatment group (High or Low SpO<sub>2</sub>) was significant for Fluctuators

**Table 3: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of NDI/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.38 (1.25-1.52)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.03 (0.69-1.53)	0.90
<b>Hypercapnic</b>	2.69 (1.82-3.96)	<0.0001
<b>Fluctuator</b>	3.07 (1.84-5.12)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.44 (1.09-1.90)	0.009

**Table 4:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of death before discharge

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.36 (1.22-1.51)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	0.90 (0.54-1.50)	0.07
<b>Hypercapnic</b>	2.47 (1.61-3.77)	<0.0001
<b>Fluctuator</b>	1.88 (1.03-3.43)	0.04
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.28 (0.94-1.74)	0.12

## Supplemental Tables

**Supplemental Tables:**

Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
PaCO <sub>2</sub> , maximum level	#	163	1098		325	971	
	Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	163	1098		325	971	
	Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
PaCO <sub>2</sub> category:	#	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
	# (%)			<0.0001			<0.0001
Hypocapnic		30 (18.4)	205 (18.7)		48 (14.8)	189 (19.5)	
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65(39.9)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	164	1106		335	979	
	High O <sub>2</sub> , # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO <sub>2</sub> DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race:	# (%)						
NH Black		55 (33.5)	421 (38.1)	0.016	112 (33.4)	376 (38.4)	0.09
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	441	659		639	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	0.015	33 (29-38)	34 (30-38)	0.25
PaCO <sub>2</sub> , maximum level	#	441	659		639	659	
	Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	438	642		625	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	441	659		639	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<0.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<0.0001
PaCO <sub>2</sub> category:	#	441	659		639	659	
Hypocapnic	# (%)	78 (17.7)	138 (20.9)	<0.0001	100 (15.7)	138 (20.9)	<0.0001
Hypercapnic		101 (22.9)	59 (9.0)		170 (26.6)	59 (9)	
Fluctuator		48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)	
Normocapnic		214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)	
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, (%)	# 223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	442	666		650	666	
	High O <sub>2</sub> , # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO <sub>2</sub> DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	0.013	221 (34)	268 (40.2)	0.02
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	0.22
Prenatal steroids	#	442	666		649	666	

<b>Characteristic</b>		<b>BPD (N=442)</b>	<b>No BPD (N=666)</b>	<b>p- value<sup>1</sup></b>	<b>Death or BPD (N=650)</b>	<b>No Death or BPD (N=666)</b>	<b>p- value<sup>1</sup></b>
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
<b>1 minute Apgar &lt; 3</b>	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
<b>5 minute Apgar &lt; 3</b>	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
<b>Prophylactic indomethacin</b>	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
<b>Vaginal delivery</b>	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	0.004	193 (29.7)	240 (36.0)	0.01

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	0.001	33 (28-38)	33 (30-38)	0.95
PaCO <sub>2</sub> , maximum level	#	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<0.0001	76 (66-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)	<0.0001
PaCO <sub>2</sub> category:	#	98	872		346	872	
Hypocapnic	# (%)	22 (22.5)	171 (19.6)	<0.0001	51 (14.7)	171 (19.6)	<0.0001
Hypercapnic		25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)		135 (39.0)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	98	878		356	878	
	High O <sub>2</sub> , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO <sub>2</sub> DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92-94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643-914)	850 (710-995)	<0.0001	734 (621-870)	850 (710-995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race:	# (%)						
NH Black		37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
NH White		37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other		3 (3.1)	30 (3.4)		14 (3.9)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 ( 26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
PaCO <sub>2</sub> , maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
PaCO <sub>2</sub> category:	#	227	991	
Hypocapnic	# (%)	26 (11.5)	196 (19.8)	<0.0001
Hypercapnic		82 (36.1)	140 (14.1)	
Fluctuator		29 (12.8)	64 (6.5)	
Normocapnic		90 (39.7)	591 (59.6)	
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	237	997	
	High O <sub>2</sub> , # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO <sub>2</sub> DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race:	# (%)			
NH Black		77(32.5)	381 (38.2)	0.26
NH White		96 (40.5)	397 (39.8)	
Hispanic		53 (22.4)	186 (18.7)	
Other		11 (4.6)	33 (3.3)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	Yes, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Inositol  
**Date:** Monday, August 12, 2013 4:53:11 PM

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Please send in your vote.

Thank you,

Stephanie

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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; (kzaterka@rti.org)  
**Subject:** Inositol

Please let me know if you do or do not want to proceed with inositol (plan would be training in October and launching thereafter)

Proceed  
 Don't proceed

Please respond by August 6

Thanks

Rose

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**Subject:** RE: comments sent to AHRQ  
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---

Feel free to share.

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Subject: Re: comments sent to AHRQ

Jon, this looks wonderful! Very well done by all who contributed. Will this be public comment, so I can forward to my IRB chair after the meeting? Kristi

>>> "Tyson, Jon E" 08/09/13 4:56 PM >>>

Fyi, comments prepared by Kathleen Kennedy, John Lantos, Susie Wootton, and me that have been sent after receiving suggestions from Wally and a number of Network folks (Neil, Carl, and Michelle) who will be attending the ORHP meeting) at the end of the month. (b)(5)

(b)(5) We hope to use this document as the basis for a manuscript and would welcome your

thoughts.

**From:** [Finer, Neil](#)  
**To:** [Shankaran, Seetha](#)  
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**Subject:** Re: PAS 2014 Proposal Submission for Topics Symposium in Ethics in Research  
**Date:** Wednesday, August 07, 2013 1:27:26 PM

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Congratulations Seetha  
Neil

On Aug 7, 2013, at 5:58 AM, "Shankaran, Seetha"  
<[sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu)<<mailto:sshankar@med.wayne.edu>>> wrote:

Hi all  
I wanted all of you to see the e-mail below—again, thanks for all your help. Will keep you posted.  
Seetha

**From:** Belinda Thomas [<mailto:bthomas@aps-spr.org>]  
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**To:** Shankaran, Seetha; [keenanwj@slu.edu](mailto:keenanwj@slu.edu)<<mailto:keenanwj@slu.edu>>  
**Subject:** PAS Proposal Notification: PAS/ASPR Joint Meeting - 2014 Vancouver, BC, Canada

<image001.jpg>

August 6, 2013

Dear Dr. Shankaran,

On behalf of the 2014 PAS Program Committee, I would like to extend our sincere appreciation for your thoughtful program proposal entitled "Ethics in the conduct of clinical/basic research" that you submitted for the PAS/ASPR Joint Meeting in Vancouver. We had a strong and extremely gratifying response from the memberships of all societies, receiving over 200 proposals.

After careful review of all submissions, the committee agreed that your proposal was one that will be of great interest to the PAS attendees and the content will contribute significantly to the strength of the Annual Meeting. While this is exciting news, it is imperative that you refrain from contacting the proposed participants at this time. Dr. William Keenan, a member of the 2014 Program Committee, will be the primary contact for this program. Dr. Keenan is included on this notification and will make contact with you shortly to convey the final content and organizational aspects to you. This includes possible chair and/or speaker replacements or additions as recommended by the committee. Please do not proceed with this program until those details and instructions have been conveyed.

We are looking forward to an exciting meeting in Vancouver next spring and greatly appreciate your program contributions.

Sincerely yours,

Dr. D. Michael Foulds

Chair, PAS Program Committee

cc: Dr. William Keenan

PAS Program Committee Member

Pediatric Academic Societies | 3400 Research Forest Dr., Suite B-7 | The Woodlands, TX 77381

Phone: 281-419-0052 | Fax: 281-419-0082 | Email: [bthomas@pas-meeting.org](mailto:bthomas@pas-meeting.org)<<mailto:bthomas@pas-meeting.org>>

| URL: [www.pas-meeting.org](http://www.pas-meeting.org)<<http://www.pas-meeting.org>>

Belinda Thomas

PAS Program Director

Information Services Manager

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www.pas-meeting.org<http://www.pas-meeting.org/>  
SAVE THE DATE: 2014 PAS/ASPR Joint Meeting ~ May 3 – 6, 2014  
From: Shankaran, Seetha  
Sent: Saturday, July 13, 2013 8:03 AM  
To: carl\_dangio@urmc.rochester.edu<mailto:carl\_dangio@urmc.rochester.edu>;  
Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; Krisa Van Meurs  
(vanmeurs@stanford.edu<mailto:vanmeurs@stanford.edu>); Barbara Stoll  
(vanmeurs@stanford.edu<mailto:vanmeurs@stanford.edu>); Barbara Stoll  
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(wtruog@cmh.edu<mailto:wtruog@cmh.edu>); Kristi Watterberg; Susan Hintz  
(srhintz@stanford.edu<mailto:srhintz@stanford.edu>); Kennedy, Kathleen A  
(Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>);  
cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>  
Cc: Shankaran, Seetha; rosemary.higgins@nih.gov<mailto:rosemary.higgins@nih.gov>  
Subject: PAS 2014 Proposal Submission for Topics Symposium in Ethics in Research

Hi all

Thank you all so much for your suggestions. This was submitted (lots of detail needed as you can see), sorry for not sending to you all earlier, have been busy on service.

Seetha

2014 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting

PROPOSAL NUMBER: 500138

PROPOSAL TYPE: Topic Symposium

Proposal Submitted by:

Seetha Shankaran, MD

Phone: 313-745-1436

Fax: 313-745-5867

Email: sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>

---

#### SESSION INFORMATION

Session Title/Topic:

Ethics in the conduct of clinical/basic research

#### Description:

This session will examine the impact of social media on practice changes in the conduct of research. The public/parental perceptions on the conduct of clinical research in pediatric patients will be discussed. The pros, cons, and risks of conducting research in today's environment will be presented. How to maintain confidentiality in the environment of social media and technology advances will be explored. The experience from trials will be reviewed and the recent public discussions regarding a multicenter neonatal study (SUPPORT) will be analyzed. The ethical aspects of conduct of research, both for new therapies compared to standard of care as well as comparative effectiveness research and waiver of consent for emergency/imminent research needs will be explored. The regulatory oversight of research, both at the governmental and local institutional level, will be presented along with the need for changes. A vigorous interactive audience participation is anticipated.

**Objective(s):**

1. To understand the ethical issues regarding conduct research in pediatric patients, including neonates
2. To understand comparative effectiveness research and waiver of consent for "emergency" research.
3. Articulate how social media impacts practice change and confidentiality concerning conduct of research.

**Session Type:**

Clinical

**Target Audience:**

Academic researchers at all stages of career and practice and across all disciplines within pediatrics

**Potential/Anticipated Audience Size:**

> 500

**Q&A/Discussion at the end of the Session (and time where applicable):**

Yes - 30 minutes

**Session Track(s):**

Academic and Research Skills

Ethics/Bioethics

Health Services Research

Media & Technology

Vulnerable and Underserved Populations

**Additional Comments:**

---

**CHAIR 1 INFORMATION**

**Suggested Person:**

Seetha Shankaran, M.D.

**Department:** Department of Pediatrics

**Institution:** Children's Hospital of Michigan

**Address 1:** 3901 Beaubien Blvd.

**Address 2:**

**City:** Detroit

**State/Province (if US or Canada):** MI

**Country:** USA

**Zip Code:** 48201

**Phone:** (313)745-1436

**Fax:** (313)745-5867

**Email:** sshankar@med.wayne.edu<<mailto:sshankar@med.wayne.edu>>

**Alternate Email:**

**Society memberships:**

AAP  
APA  
APS  
SPR

**Will this Chair give an Overview:**

Yes

**Length of Overview:**

5 minutes

**Overview Title:**

Introduction of speakers

---

**TOPIC 1 INFORMATION**

**Suggested Person:**

Carl T. D'Angio, MD

**Department:** Department of Pediatrics

**Institution:** University of Rochester

**Address 1:** 601 Elmwood Avenue, Box 651

**Address 2:**

**City:** Rochester

**State/Province (if US or Canada):** NY

**Country:** USA

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**Phone:** (585)273-4911

**Fax:** (585) 461-3614

**Email:** Carl\_Dangio@urmc.rochester.edu<[mailto:Carl\\_Dangio@urmc.rochester.edu](mailto:Carl_Dangio@urmc.rochester.edu)>

**Alternate Email:**

**Society memberships:**

AAP  
APA  
SPR

**Presentation Title:**

Background for this session: the SUPPORT study

**Length of Lecture:**

5 minutes

QA/Discussion time following this particular Lecture:

No

---

TOPIC 2 INFORMATION

Suggested Person:

Robin H. Steinhorn, M.D.

Department: Department of Pediatrics

Institution: UC Davis School of Medicine

Address 1: 2516 Stockton Blvd.

Address 2:

City: Sacramento

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Fax:

Email: rsteinhorn@ucdavis.edu<<mailto:rsteinhorn@ucdavis.edu>>

Alternate Email:

Society memberships:

AAP

APA

APS

SPR

Presentation Title:

How Social Media and public discussion impacts conduct of clinical trials

Length of Lecture:

15 minutes

QA/Discussion time following this particular Lecture:

Yes

Length of QA/Discussion time:

5 minutes

---

TOPIC 3 INFORMATION

**Suggested Person:**  
John D. Lantos, M.D.

**Department:** Department of Bioethics and General Pediatrics

**Institution:** Children's Mercy Hosp and University of Missouri a

**Address 1:** 2401 Gillham Road

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**Country:** usa

**Zip Code:** 64108

**Phone:** 816-701-5283

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**Email:** jlantos@cmh.edu<<mailto:jlantos@cmh.edu>>

**Alternate Email:**

**Society memberships:**

AAP

APA

APS

SPR

**Presentation Title:**

Role of Ethics in the conduct of research in pediatrics in today's climate of social media and technology

**Length of Lecture:**

15 minutes

**QA/Discussion time following this particular Lecture:**

Yes

**Length of QA/Discussion time:**

5 minutes

---

#### TOPIC 4 INFORMATION

**Suggested Person:**

Robert Califf

**Department:** Duke Translational Medicine institute

**Institution:** Duke University Medical Center

**Address 1:** 1121 Davison Building, Duke South

Address 2:

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Email: Robert.califf@duke.edu<<mailto:Robert.califf@duke.edu>>

Alternate Email:

Society memberships:

No society memberships

Explanation for this non-member selection:

American College of Cardiology

American College of Physicians

American Medical Association

American Society of Clinical Investigation

Argentine Society of Cardiology

Association of American Physicians

Drug Information Association

Society for Clinical Epidemiology and Health Care Research

American Heart Association

Association of University Cardiologists

European Society of Cardiology

Association of American Physicians

American Society of Clinical Investigators

Society for Clinical Trials, Inc

Presentation Title:

Comparative Effectiveness research, new therapies and waiver of consent

Length of Lecture:

15 minutes

QA/Discussion time following this particular Lecture:

Yes

Length of QA/Discussion time:

5 minutes

---

#### TOPIC 5 INFORMATION

Suggested Person:

Mildred Solomon, EdD

Department: Global Health and Social Medicine, Division of Medical Ethics'

**Institution:** Harvard Medical School

**Address 1:** 641 Huntington Avenue

**Address 2:**

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**Country:** USA

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**Alternate Email:**

**Society memberships:**

No society memberships

**Explanation for this non-member selection:**

AAP

**Presentation Title:**

Regulatory oversight of research in pediatrics: Do we need changes?

**Length of Lecture:**

15 minutes

**QA/Discussion time following this particular Lecture:**

Yes

**Length of QA/Discussion time:**

5 minutes

---

#### TOPIC 6 INFORMATION

**Suggested Person:**

Paul Costello

**Department:** School of Medicine - Communications & Public Affairs

**Institution:** Stanford University

**Address 1:** 3172 Porter Drive

**Address 2:**

**City:** Palo Alto,

State/Province (if US or Canada): California

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Alternate Email:

Society memberships:

No society memberships

Explanation for this non-member selection:

AAP

Presentation Title:

The role of social media in changing the landscape of research

Length of Lecture:

15 minutes

QA/Discussion time following this particular Lecture:

Yes

Length of QA/Discussion time:

5 minutes

[Print]

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**From:** Walsh, Michele  
**To:** Finer, Neil; Tyson, Jon E  
**Cc:** D'Angio, Carl (Carl\_Dangio@URMC.Rochester.edu) (Carl\_Dangio@URMC.Rochester.edu); Lantos, John (jlantos@cmh.edu); Kennedy, Kathleen A; Wootton, Susan H; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: document to be submitted to AHRQ for upcoming meeting  
**Date:** Wednesday, August 07, 2013 11:47:23 AM  
**Attachments:** OHRP\_CE research Aug 6 mw comment.docx

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Jon: I think your comments are well thought out  
And diplomatically made.  
I attach a few minor embedded comments.  
If I can meet the deadline today I may send comments-  
But on service and having trouble getting the time to  
Submit.

Michele Walsh  
Chief Division of Neonatology  
Rainbow Babies & Childrens Hospital  
Professor of Pediatrics  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu  
Phone: (216) 844-3387  
Fax: (216) 844-3380

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Wednesday, August 07, 2013 9:48 AM  
To: Tyson, Jon E  
Cc: Walsh, Michele; D'Angio, Carl (Carl\_Dangio@URMC.Rochester.edu) (Carl\_Dangio@URMC.Rochester.edu); Lantos, John (jlantos@cmh.edu); Kennedy, Kathleen A; Wootton, Susan H; Rose Higgins MD (higginsr@mail.nih.gov)  
Subject: Re: document to be submitted to AHRQ for upcoming meeting

Hi Jon  
I will not be making an application to speak at this meeting  
If there are issues or questions that I can address in the discussion, I will try to respond  
Neil

On Aug 7, 2013, at 6:24 AM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu> wrote:

> Have you decided what question(s) you want to speak about in the public discussion at the OHRP meeting?

>

>

> \_\_\_\_\_  
> From: Tyson, Jon E  
> Sent: Tuesday, August 06, 2013 11:02 AM  
> To: Neil N Finer; Walsh, Michele (Michele.Walsh@UHhospitals.org); D'Angio, Carl (Carl\_Dangio@URMC.Rochester.edu) (Carl\_Dangio@URMC.Rochester.edu); Rose Higgins MD (higginsr@mail.nih.gov)  
> Cc: Lantos, John (jlantos@cmh.edu); Kennedy, Kathleen A; Wootton, Susan H  
> Subject: document to be submitted to AHRQ for upcoming meeting  
>

> This was developed by Kathleen Kennedy, John Lantos, Susie Wootton (one of my mentees interested in research ethics), and me. I am sending it to you as Network participants who are planning to attend the AHRQ meeting.  
> While I was not at the last Steering Committee meeting, I have taken Kathleen's advice to remove all discussion of

SUPPORT from the document, largely to increase the receptivity of AHRQ to our comments. However, you will see that the comments and recommendations fully support what was done in SUPPORT. I need to submit tomorrow. If you have time, we would of course welcome any suggestions for this or what I hope will be a later manuscript that will include a discussion about SUPPORT.

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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

Our comments are focused on comparative effectiveness (CE) trials. CE trials compare outcomes for patients randomized to different treatment methods or management strategies used in clinical practice. CE trials differ from those for which current regulatory requirements for randomized trials were developed: trials comparing patients randomized to receive a new experimental intervention with control patients who receive conventional treatment or in some cases, a placebo or no treatment. The key difference is that CE trials have no "experimental" arm and no "control" arm and that the potential risks in one arm are the potential benefits of the other and vice versa.

**1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?**

This question and others that follow would be clearer and more meaningful if the term "standard of care" was removed or carefully limited to therapies demonstrated to be beneficial (as judged by criteria like the GRADE criteria<sup>1,2</sup> or those of the U.S. Preventive Services Task Force<sup>3</sup>). This term causes confusion when applied to unproven but routinely or commonly used therapies or treatment strategies which unfortunately make up the great majority of therapies used in clinical practice.<sup>4,5,6,7</sup> The fact that most treatments fall in this category highlights the pressing need to promote CE trials and a learning health care system.<sup>8,9,10</sup> To call one treatment or another "standard of care" misrepresents the very problem that policies for oversight of CE trials must solve. Such therapies would be better described by terms like "usual care" or "conventional treatment."

The first step for IRBs is to ask "Is the proposed trial justified?" CE trials are justified when there is inadequate evidence to determine the best treatment method for the patients to be studied. This decision may not be easy and may well require expertise in the clinical issue under investigation or in study design or interpretation.<sup>11</sup>

The trial should be deemed justified when the best available evidence indicates no clear overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied. CE trials should not be performed if there already is strong evidence from a proper systematic review of prior randomized trials<sup>12</sup> (indicating that one of the therapies to be studied is superior to the other). Such evidence may not be recognized without this kind of review. An exception might be considered if a compelling argument could be made that evidence from prior trials may not be generalizable to current practice. In the absence of prior trials, the need for a CE trial should be challenged if a well done cohort study has identified evidence of either strong benefit or hazard (a relative risk for an adverse outcome that is either  $\leq 0.10$  or  $\geq 10$ ) for one treatment method to be studied relative to the other.<sup>13</sup> Otherwise, observational studies may be quite misleading and are usually an inadequate basis to conclude that a CE trial is unwarranted.

Therapies are ordinarily first evaluated in efficacy trials (to assess therapies under ideal or restricted circumstances). Therapies found to be beneficial in efficacy trials then need evaluation in effectiveness trials (to assess therapies in routine clinical circumstances). Therapies that are clearly beneficial but quite expensive may also be considered as appropriate for CE trials. In such situations, the trials would be designed to assess whether such therapies are reasonably cost effective for general use or limited use in highly selected centers or patient populations.

**Comment [A1]:** Do you need to explain efficacy and effectiveness? Not sure OHRP staff will understand this.

**a. Under what circumstances should an IRB consider those to be risks that may result from the research?**

The Common Rule states that the risks of research are the incremental risks from participation in research, as compared to the risks that would be experienced without study participation. In a legitimate CE trial the treatments under investigation are already used in clinical practice, and there is no predictable or reasonably foreseeable overall difference in their risks (relative to the benefits) as assessed from the best available evidence. So any differences in outcomes observed in the trial result from nonpredictable treatment risks or baseline differences in disease severity and are not from the risks of the research itself.

Systematic reviews of outcomes for patients in well-designed RCTs provide no evidence that participation in a trial, compared to non-participation in the trial, increases the actual risks of adverse outcomes identified at the completion of the trial.<sup>14,15</sup> Thus, there is no empiric basis to assume that CE trials compromise the outcome of participants for the benefit of future patients. Physicians who conduct such trials are committed to the welfare of the patients. If they knew the best treatment for these patients, they would provide it. In some trials, patient risk may be reduced by the investigators' efforts to most effectively provide the therapies under investigation, to optimize the patient's supportive care and clinical monitoring, and to minimize and more quickly identify and address treatment hazards or disease complications than would occur in clinical practice.

**b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?**

As noted by OHRP, the IRB is to consider research risks to be only the risks and benefits that may result from the research (as distinguished from those that participants would incur even if not participating in research). In many studies, those risks are easily identifiable. They include risks from extra blood drawing, biopsies, or other procedures imposed by the study that would not ordinarily be done in routine clinical care. The IRB should consider these risks to be related to the research. They should not consider the risks of being assigned to one

arm or the other of a CE trial to be a risk of research, even if, as a result of the study, the chances that a particular patient receives one therapy or another may be different if they are in the study compared to if they are not.

The specific risks of the individual therapies under investigation are likely to differ. However, the IRB's agreement that the trial is justified indicates agreement that there is no predictable overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied as judged from the best available evidence.

**c. What type of evidence should an IRB evaluate in identifying these risks?**

The IRB should evaluate the methodologically strongest relevant evidence in assessing the need for the trial and in identifying the specific risks of the individual therapies under investigation. The investigators should reference and describe the findings of any systematic review of all relevant randomized trials (particularly the well performed reviews of the Cochrane Collaboration). Unless refuted by rigorous randomized trials, evidence about treatment risks from well performed cohort or case-control studies may also be considered.

Even in randomized trials, the available evidence is not always easily interpreted, particularly when the proposed trial involves populations or circumstances not previously assessed or when offsetting benefits and hazards or evidence of subgroup differences or treatment heterogeneity are identified in prior trials. As noted above, criteria like the GRADE criteria or those of the Preventive Task Force may help in evaluating and integrating the available evidence. The AGREE II criteria<sup>18,17</sup> may be helpful in evaluating the evidence underlying practice guidelines. IRBs, like investigators and clinicians, will need to stay abreast of methods being developed or used to evaluate when the treatment hazards outweigh the benefits for individual patients or patient subgroups.<sup>18,19</sup>

**2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?**

We see a number of issues that need to be considered:

**A. The available evidence about potential treatment hazards.** Potential risks that can be considered to be reasonably foreseeable would include a) biologically plausible treatment hazards that have not been well assessed in clinical studies, and b) hazards that have been evaluated in a systematic review of relevant clinical trials or in the absence of such a review, in one or more clinical trials or well performed cohort studies and found to marginally or significantly associated with the treatment ( $p < 0.10$ ). In accordance with the principles of evidence-based medicine, investigators should not be required to list on a consent form all possible hazards or hazards that are not close to significant ( $p > 0.10$ ) in systematic reviews or in well performed clinical trials or cohort studies. To deem such potential hazards as "reasonably foreseeable" would require investigators to list almost any hazard that that could be considered minimally plausible despite evidence to the contrary. This might more often mislead than inform potential research participants or their surrogates. Listing all potential minor or rare hazards would also distract attention from hazards of greater importance to patients.

Foreseeable treatment risks often do not include some or many of the secondary outcomes listed in the protocol. Investigators often specify exhaustive lists of secondary outcomes for CE trials to ensure that all potentially important outcomes are carefully monitored and recorded and that unexpected observed differences are accepted by reviewers as "pre-specified" outcomes. Whether these should be listed as risks hinges on the available evidence as noted above.

**B. Risk disclosure with competing outcomes.** From the public health perspective, the most important CER studies assess primary outcomes important to patients, e.g., heart attacks or strokes, rather than short-term changes in things like blood pressure or laboratory tests. Study participants often must be monitored for long periods of time to evaluate these outcomes. If the participants are at high risk for death, as would be the case for elderly adults or small premature infants, some or many may die before they have to opportunity to develop such outcomes. In this circumstance, death is thus a competing outcome that prevents the identification of other adverse outcomes. For this reason, it is often prudent to include death in the primary outcome (e.g. heart attack, stroke, or death) even though the investigators may have no reason to think that the different treatments would result in a difference in mortality. Including death in the primary outcome can prove to be particularly fortunate if, as sometimes happens, one of the treatments under investigation is associated with an increased mortality rate despite reducing other adverse outcomes like heart attacks or strokes.<sup>20</sup> However, the inclusion of death in the primary outcome should not be assumed to indicate that a higher mortality is foreseeable based on the best available evidence or should be noted on the consent form as a foreseeable risk for either treatment group.

**C. A need for individualized consent forms?** It might be argued that incremental risks and benefits of study participation should be disclosed in comparison to the treatment that each individual participant would otherwise receive. However, this approach is unlikely to be feasible. Clinicians' treatment preferences often vary by provider, may be variable or change over time, and may not be known at enrollment. Efforts to individualize the consent form would lead to troublesome differences in the forms within and across different study sites. For these reasons, the risks and benefits of

participation cannot be listed in separate "risks" and "benefits" sections of a typical consent form template. The "risks" of one study strategy (higher risk of xxx) are "benefits" (lower risk of xxx) for the other strategy. A better approach would be to inform subjects in a straightforward manner of the prevailing practice variation and explain why researchers believe that randomization is appropriate. This information would be the same for all subjects and would be consistent with the IRB's approval of the study as a legitimate CE trial.

4. *The need to develop better and more uniform approaches to risk disclosure in both research and clinical practice. The appropriate risk disclosure in a CE trial, as in clinical care using the same therapy, needs to be more clearly defined in studies of such issues as patient wants, needs, and comprehension in routine and emergent circumstances; the effects of differing approaches to risk disclosure (including nocebo effects<sup>21</sup>); and factors that can augment the validity of informed consent. It is difficult to see how any ethical principles including respect for persons, beneficence, or justice justify a different level of risk disclosure in clinical practice and clinical research for patients receiving the same unproven treatment method. There also seem to be no data to indicate that well informed patients support this double standard.*

Comment [A2]: this gets to be hard to follow.

**3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk?**

*Randomization should not be considered to increase risk in legitimate CE trials because:*

A. *As discussed above, randomization to alternative treatment methods in such trials has no foreseeable effect on treatment risks for participants in the trial.*

*Randomization is simply a tool to avoid differences in baseline risk between treatment groups that are a notorious cause of confounding in observational studies comparing different therapies. It thus reduces the possibility of misleading results and erroneous conclusions but has no effect on the risks of the treatments provided.*

*In many clinical circumstances, there is inadequate relevant evidence to determine which of a number of commonly used treatments is preferable. In those circumstances, the treatment that is chosen will depend on happenstance and vary as a result of such factors as where the patient happens to be treated, who the treating physician happens to be, and what his or her treatment preferences happen to be. Those treatment preferences may reflect the considerations of an extremely dedicated, well informed, and appropriately uncertain physician. Alternatively, it may be based on the physician's vague recall of the relevant research, a clinical anecdote, a casual conversation with colleagues, or a recent visit from a drug company representative. It may be a combination of these factors. The net result, in the absence of good evidence from good clinical trials, is a decision that at best is similar to a mental flip-of-the-coin*

B. *The unfounded assumption that clinical trials increase risk leads to associated regulatory requirements to warn patients of dubious or non-existent risks. This may inadvertently harm patients by disincentivizing proper testing and incentivizing clinical use of unproven and possibly hazardous therapies.*

*As indicated below, this effect can have major serious adverse consequences that should be carefully considered.*

**Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?**

*Providing the CE trial is justified, waiver would be allowable in some circumstances,<sup>22,23,24,25</sup> and well justified in urgent or emergent circumstances when valid consent cannot be reasonably obtained and when treatment delays to obtain consent (~ 1 hour, if not longer, in many trials) would be expected to alter the treatment benefits or hazards. This approach would expand the current criteria to allow waiver of consent when the treatment is not considered potentially life-saving and remove the requirement for community participation in these circumstances. Patients receiving proven emergency therapies benefit from prior studies, and their participation in well justified CE research are needed to further improve outcomes. Requiring consent in these circumstances can A) increase the morbidity or mortality of trial participants,<sup>26,27</sup> B) result in erroneous conclusions that adversely affect the care and outcome of a very large number of future patients; C) delay completion of a valid trial and dissemination of truly beneficial therapies or abandonment of truly harmful therapies in clinical practice. Requiring consent in these circumstances violates the principle of beneficence and arguably, also respect for persons and justice.*

*Public understanding of CER in these circumstances could be promoted by including potential study participants in the process of study design as well as by rigorous efforts to explain to participants who have been enrolled in trials of emergency therapies without their consent - in as timely manner as possible - the rationale for the study and the reasons why they or their loved one was enrolled. At that time, investigators should also seek the patient's consent to continue in the trial or to allow use of their data.*

*Whatever disclosure and consent procedures are required for CER trials, we would urge that they should be similar for all patients receiving the same unproven therapy whether as part of routine clinical care, a prospective observational study, or a randomized trial. As we have argued elsewhere,<sup>28</sup> consent procedures deserve reconsideration for clinical as well as research use of unproven therapies, particularly new unproven therapies. As Fost has emphasized, it is not plausible to*

presume that a patient would want a therapy never properly tested for safety or efficacy with no prior review, but would object to the same treatment being given with all the safeguards of a controlled trial. The current double standard for both risk disclosure and written consent inadvertently discourages proper testing, encourages clinical administration of unproven therapies, and contributes to the all-too-common problem that unproven therapies are widely used for years or even decades before they are rigorously evaluated and found to be ineffective or harmful.<sup>5,28,29,30</sup>

**4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions?**

The uncertainty about risk is influenced by the quality of the prior research, the *p* values and confidence intervals for the measures of treatment effect (relative risk, risk difference, and number needed to treat or number needed to harm), and in some studies, Bayesian estimates of the probability of specific treatment effects. The discussion above indicates how this uncertainty may be judged in addressing these questions. To the extent feasible, the level of uncertainty should be conveyed to study subjects, but optimal methods have not been developed for conveying these complex concepts to patients with variable skills in literacy and numeracy.

**What if the risk significantly varies within the standard of care?**

As noted above, the trial is not justified if the relationship of risks to benefits has been shown to be more favorable in one treatment group than the other(s). Suggestions are detailed above for disclosing risks and benefits or advantages and disadvantages of different study strategies that are within the range of common practice.

**5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases risk of harm, or is it necessary that there be published studies identifying the risk?**

It is unclear what is meant by "documented beliefs." However, the beliefs within the medical community about an intervention can vary widely, particularly if they have not been well assessed in randomized trials. As evident from the long unfortunate history of oxygen administration to premature infants,<sup>31,32</sup> the evidence supporting the treatment is more important than the level of belief among some or many physicians.

As noted above, potential treatment risks need not be disclosed if they were well assessed and shown to have no association in relevant clinical trials of these therapies, or in the absence of these trials, in well performed cohort studies. Biologically plausible potential treatment hazards that have not been assessed in clinical studies should ordinarily be disclosed if they would be of concern to a sizable proportion of patients.

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**From:** Stevens, Timothy  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Newman, Jamie <newman@rti.org> (newman@rti.org)  
**Subject:** FW: PEDIATRICS: Decision Letter for MS ID 2013-0756.R1  
**Date:** Monday, August 05, 2013 9:33:02 AM

---

FYI

I thought I'd try J Peds next.

Can you please forward to the co-authors?

Thanks

Tim

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

From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com  
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of  
PediatricsEditorial@aap.org  
Sent: Monday, August 05, 2013 9:08 AM  
To: Stevens, Timothy  
Subject: PEDIATRICS: Decision Letter for MS ID 2013-0756.R1

05-Aug-2013

RE: MS ID 2013-0756.R1

Respiratory Outcomes of the Surfactant Positive Pressure and Oximetry Randomized Trial (SUPPORT)

Dear Dr. Stevens:

Thank you for submitting your manuscript to Pediatrics. We are sorry that we are not accepting it for publication. Because of the large number of submissions, the editors must reject many worthy manuscripts. Rejection reflects the priorities of the journal; it does not necessarily indicate that your manuscript is unsuitable for publication elsewhere.

Comments from our reviewers are included below. Reviewer input is one of several factors involved in making decisions on papers. Because of space limitations, even papers receiving positive comments from the reviewers are often rejected.

We look forward to receiving other articles from you in the future.

Sincerely,

Lewis R. First, MD  
Editor-in-Chief, Pediatrics  
Professor and Chair, Department of Pediatrics University of Vermont, College of Medicine Chief of Pediatrics,  
Vermont Children's Hospital at Fletcher Allen Health Care  
802-656-0027 (office)  
802-656-2077 (fax)  
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Page 1694 of 2000

Withheld pursuant to exemption

(b)(4),(b)(6)

of the Freedom of Information and Privacy Act

**Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Friday, August 02, 2013 9:01 AM  
**To:** Spong, Catherine (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]  
**Cc:** Kaeser, Lisa (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]  
**Subject:** FW: Letter regarding use of experimental pulse oximeter devices in the SUPPORT study

FYI...

Alan

**From:** Michael Carome [<mailto:mcarome@citizen.org>]  
**Sent:** Friday, August 02, 2013 8:57 AM  
**To:** Shuren, Jeff (FDA/CDRH)  
**Cc:** Hamburg, Margaret A. (FDA); Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Menikoff, Jerry (HHS/OASH); Børror, Kristina C (HHS/OASH)  
**Subject:** Letter regarding use of experimental pulse oximeter devices in the SUPPORT study

Dear Dr. Shuren,

Please find attached a letter asking the Food and Drug Administration to investigate issues related to the use of experimental pulse oximeter devices in the SUPPORT study, a clinical trial that involved extremely premature infants. The original hardcopy will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.  
Director, Health Research Group  
Public Citizen  
1600 20th Street, NW  
Washington, DC 20009

Tele: 202-588-7781  
Fax: 202-588-7796  
email: [mcarome@citizen.org](mailto:mcarome@citizen.org)  
web: [www.citizen.org](http://www.citizen.org)

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Michael Carome <mcarome@citizen.org>  
**Sent:** Friday, August 02, 2013 8:57 AM  
**To:** Shuren, Jeff (FDA/CDRH)  
**Cc:** Hamburg, Margaret A. (FDA); Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Menikoff, Jerry (HHS/OASH); Borrer, Kristina C (HHS/OASH)  
**Subject:** Letter regarding use of experimental pulse oximeter devices in the SUPPORT study  
**Attachments:** 130802\_Letter to FDA re SUPPORT Study Pulse Oximeters\_FINAL\_Signed.pdf

Dear Dr. Shuren,

Please find attached a letter asking the Food and Drug Administration to investigate issues related to the use of experimental pulse oximeter devices in the SUPPORT study, a clinical trial that involved extremely premature infants. The original hardcopy will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.  
Director, Health Research Group  
Public Citizen  
1600 20th Street, NW  
Washington, DC 20009

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August 2, 2013

Jeffrey E. Shuren, M.D., J.D.  
Director, Center for Devices and Radiological Health  
Food and Drug Administration  
Department of Health and Human Services  
WO 66, Room 5442  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**RE: The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

Dear Dr. Shuren:

As you may be aware, Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, sent letters to Secretary of Health and Human Services Kathleen Sebelius on April 10 and May 8, 2013, raising serious concerns about the SUPPORT study funded by the National Institutes of Health (NIH) and conducted by approximately two dozen academic medical institutions of the Neonatal Research Network.<sup>1,2</sup> Our letters to the Secretary highlighted important and material factual omissions — as well as many misleading statements — regarding the purpose, nature, and risks of the research in all consent forms approved by the institutional review boards (IRBs) that reviewed and approved this study.

We are writing to you now to request that the Food and Drug Administration (FDA) investigate issues related to the experimental pulse oximeter devices used in the SUPPORT study and the inclusion of one particularly misleading statement in many of the IRB-approved SUPPORT study consent forms regarding these devices. At the direction of the SUPPORT study investigators for the purposes of the research, the manufacturer of these pulse oximeters, the Masimo, intentionally miscalibrated the oximeters so that they would display either falsely low or falsely high oxygen saturation levels when the actual oxygen saturation level was between 85 and 95 percent (see enclosed letter). However, nine of the 22 IRB-approved consent forms obtained from NIH by Public Citizen misleadingly stated that the experimental pulse oximeters used in the research were “FDA-approved.” In conducting its investigation, we urge the FDA to address the following questions:

---

<sup>1</sup> Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. April 10, 2013. <http://www.citizen.org/documents/2111.pdf>. August 1, 2013.

<sup>2</sup> Carome MA, Wolfe SM, Macklin R. Letter and report to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. May 8, 2013. <http://www.citizen.org/documents/2124.pdf>. Accessed August 1, 2013.

Public Citizen

August 2, 2013, Letter to the FDA on Pulse Oximeter  
Devices Used in SUPPORT Study

- (1) Did Masimo or the SUPPORT study investigators contact the FDA and seek approval to use these intentionally miscalibrated experimental pulse oximeters in clinical trials? If not, should they have?
- (2) Did use of the experimentally altered pulse oximeters in the study require FDA approval of an investigational device exemption (IDE)?
- (3) Did the inclusion of the misleading statement in the IRB-approved consent forms indicating that the pulse oximeters were FDA-approved violate the FDA's human subjects protection regulations?

### Background

The SUPPORT study involved 1,316 extremely premature infants enrolled between 2005 and 2009 at more than 20 prominent medical research centers throughout the U.S.<sup>3</sup> The study comprised two simultaneous experiments. In one experiment, the babies were randomly divided into two groups that each received a different treatment to assist their breathing (ventilation of the lungs) following delivery.<sup>4</sup> In the other, simultaneous experiment, which is the primary focus of this letter, babies were further randomly divided between a low-oxygen group and a high-oxygen group.<sup>5</sup> For the low-oxygen group, the SUPPORT study investigators tried to maintain the babies' blood oxygen levels in a low target range (oxygen saturation level of 85 to 89 percent) and for the high-oxygen group in a high target range (oxygen saturation level of 91 to 95 percent). The researchers then measured the impact of the two target ranges of oxygen levels for premature babies – specifically, whether infants in one group were more likely to die, suffer brain damage, or develop an eye disease called retinopathy of prematurity and blindness in comparison to the other group.

### Use of Experimental Pulse Oximeter Devices

The study design used an experimental procedure under which the entire medical team caring for each premature baby in the study was intentionally given inaccurate information about the baby's blood oxygen saturation levels by using experimental pulse oximeter devices that were miscalibrated across the wide range of oxygen saturations between 85% and 95%. These experimental devices were used for the entire time the babies were on supplemental oxygen.

The use of these experimental pulse oximeters is explained in the following excerpts from the SUPPORT study protocol:<sup>6</sup>

---

<sup>3</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.

<sup>4</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely premature infants. *N Engl J Med.* 2010;362(21):1970-1979.

<sup>5</sup> SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med.* 2010;362(21):1959-1969.

<sup>6</sup> NICHD Neonatal Research Network. The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants: The SUPPORT trial. August 28, 2004 (revised September 16, 2004; updated March 28, 2005). <http://www.nih.gov/icd/od/foia/library/Protocol.pdf>. Accessed August 1, 2013.

(Page 12, section 3.7, Randomization) 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 [actual] Pulse Oximeter Range...** [Emphasis added]

(Page 17, 4.1 B Study Intervention: Low versus High SpO<sub>2</sub> Range) There will be 2 ranges of SpO<sub>2</sub> 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 SpO<sub>2</sub> ranges are in the Target ranges indicated above. Thus a Low range PO will read 88% when the actual SpO<sub>2</sub> is approximately 86%, and 92% when the actual SpO<sub>2</sub> is 89%. Similarly the High range PO will display 88% when the actual SpO<sub>2</sub> is 91% and indicate 92% when the actual SpO<sub>2</sub> is approximately 95%. 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 revert to the actual SpO<sub>2</sub> values and allow the caretakers to be aware of actual SpO<sub>2</sub> values < 85% and > 95%.

Note that for any displayed oxygen saturation level between 88% and 92%, the absolute difference between the actual oxygen saturation levels for the high- versus low-oxygen groups was 6%. For example, when the *displayed* oxygen level was 90%, the *true* oxygen level was 93% for the high-oxygen group and 87% for the low-oxygen group.

Disturbingly, the SUPPORT study protocol offered no evidence that it was safe to use these miscalibrated experimental medical devices that provided the entire medical teams caring for these critically ill premature babies with inaccurate information regarding oxygen saturation levels. Because of the inaccurately high oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the low-oxygen experimental group, it is plausible that the medical team may have treated some critically ill babies with too little oxygen, potentially resulting in brain injury and death secondary to hypoxemia (deficient oxygen). In contrast, because of the inaccurately low oxygenation saturation values provided to the medical team by the pulse oximeters for babies in the high-oxygen experimental group, it is also plausible that the medical team may have treated those babies with more oxygen than they needed, resulting in severe retinopathy of prematurity, requiring surgery and possibly causing blindness.

### **Misleading Statement in the IRB-Approved Consent Forms**

The miscalibrated experimental pulse oximeters used in the SUPPORT study certainly could not be considered in any way to be "FDA-approved." And yet, our review of the IRB-approved study consent forms revealed that nine of them included a statement identical or very similar to the following:<sup>7</sup>

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<sup>7</sup> IRB-approved consent forms for the SUPPORT study. <http://www.citizen.org/documents/support-study-consent-form.pdf>. Accessed August 1, 2013.

Public Citizen

August 2, 2013, Letter to the FDA on Pulse Oximeter  
Devices Used in SUPPORT Study

The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes.

The consent forms that included such a statement were approved by the IRBs for the following institutions:<sup>8</sup>

- Duke University Health System
- Stanford University School of Medicine
- Tufts Medical Center
- University of California, San Diego
- University of New Mexico Health Sciences Center
- University of Texas Health Science Center, Houston
- University of Texas Southwestern Medical Center at Dallas
- Wayne State University
- Women and Infants Hospital of Rhode Island

To state that these devices were FDA-approved was misleading and only served to provide false assurances about the safety of the experiment to the parents of premature infants enrolled in the study. The consent forms instead should have informed parents of prospective subjects that the pulse oximeters being used in the study: (a) were experimental devices, (b) would never have been used in routine clinical care of critically ill premature babies, and (c) had **not** been approved by the FDA for use in a clinical care or research setting.

#### **Conclusions and Summary of Requested Actions**

In conclusion, the use of the experimental pulse oximeter devices during the conduct of the SUPPORT study raises important questions regarding compliance with FDA medical device regulations. Furthermore, the misleading statement that the experimental pulse oximeters being used in the research were "FDA-approved" was among the many serious problems with consent process for the SUPPORT study. These problems ultimately resulted in a failure of the investigators to obtain the legally effective informed consent of the parents of the subjects enrolled in the study, thus making the conduct of the study highly unethical.

We therefore request that the FDA investigate issues related to the experimental pulse oximeter devices used in the SUPPORT study and the inclusion of the misleading statement in the IRB-approved SUPPORT study consent forms indicating that these devices were FDA-approved. In conducting its investigation, we urge the FDA to address the following questions:

- (1) Did Masimo or the SUPPORT study investigators contact the FDA and seek approval to use these intentionally miscalibrated experimental pulse oximeters in clinical trials? If not, should they have?

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<sup>8</sup> *Ibid.*

Public Citizen

August 2, 2013, Letter to the FDA on Pulse Oximeter  
Devices Used in SUPPORT Study

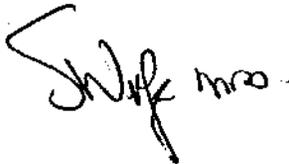
- (2) Did use of the experimentally altered pulse oximeters in the study require FDA approval of an IDE?
- (3) Did the misleading statements in the IRB-approved consent forms indicating that the pulse oximeters were FDA-approved violate the FDA's human subjects protection regulations?

Thank you for your prompt attention to these important human subjects research issues. Please contact us if you have any questions or need additional information.

Sincerely,



Michael A. Carome, M.D.  
Director  
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.  
Founder and Senior Adviser  
Public Citizen's Health Research Group

Enclosure: June 30, 2004, letter from Masimo

cc: Dr. Margaret Hamburg, Commissioner, FDA  
Dr. Francis Collins, Director, NIH  
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Development  
Dr. Jerry Menikoff, Director, OHRP  
Dr. Kristina Borrer, Director, Division of Compliance Oversight, OHRP

**MASIMO**

40 Park  
Irvine, CA 92618  
Tel: 949-297-7000  
Fax: 949-297-7001

June 30, 2004

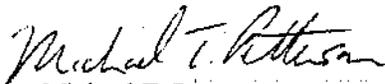
To Whom It May Concern:

This letter is to inform the reader about the modifications performed on the Masimo SET Radical Pulse Oximeter to be used in an NICHD Neonatal Network trial entitled "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) Trial". This study, lead by Dr. Neil Finer (UCSD) will evaluate two oxygenation ranges on infants immediately after birth and during their hospital stay. In order to mask the oxygenation ranges from the clinicians in the study, these researchers have asked Masimo Corporation to slightly alter the reading displayed on the Masimo Radical pulse oximeter between the 84% to 96% range. One group of pulse oximeters will read approximately 3% higher than the actual number while the other group of pulse oximeters will read approximately 3% low in this range. The researchers have required that the actual number be displayed below 85% and above 95%. The alarm will sound at 84% and 96%.

Masimo has performed validation tests on this software and found it works per the researchers' request. In addition, all alarms and error messages are still intact and active.

Masimo was willing to mask the pulse oximeters per the researchers' instructions since the intended ranges used in the study are in common use in Neonatal Intensive Care Units (NICUs) across the country. This study is aimed at refining the guidelines as to the best oxygen management range for neonates.

Respectfully,



Michael T. Petterson  
Sr. Director, Clinical Research  
Masimo Corporation



James Cronin  
Vice President, Regulatory Affairs  
Masimo Corporation  
Irvine, CA

Masimo Corporation

**From:** [Namasivayam Ambalavanan](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Data from AuthorshipResponsibility\_PCO2\_SUPPORT  
**Date:** Thursday, August 01, 2013 3:03:13 PM

---

Thank you!  
Ambal

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

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Thursday, August 01, 2013 2:02 PM  
**To:** Namasivayam Ambalavanan  
**Subject:** Data from AuthorshipResponsibility\_PCO2\_SUPPORT

Ambal - Here is my form

Thanks  
Rose

The attached file contains data that was entered into a form. It is not the form itself.

The recipient of this data file should save it locally with a unique name. Adobe Acrobat Professional 7 or later can process this data by importing it back into the blank form or creating a spreadsheet from several data files. See Help in Adobe Acrobat Professional 7 or later for more details.

**From:** Namasivayam Ambalavanan  
**To:** Shankaran, Seetha; Kennedy, Kathleen A; Michael Cotten, M.D.  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Namasivayam Ambalavanan; Namasivayam Ambalavanan  
**Subject:** RE: PaCO2 manuscript : Fifth draft of August 1, 2013 + Authorship Acknowledgement  
**Date:** Thursday, August 01, 2013 2:52:11 PM  
**Attachments:** PCO2 SUPPORT Aug1 2013.docx  
AuthorshipResponsibility PCO2 SUPPORT.pdf  
**Importance:** High

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Dear All,

Thank you for your comments on the previous drafts. Attached is the fifth draft of our manuscript evaluating PCO2 in SUPPORT. There are minor changes since the previous draft. The paper has been formatted for PEDIATRICS. The word count is a bit high (3075 rather than 3000), so will need a little trimming. Also attached is the Authorship Agreement – please complete and email (click the button on form to automatically email it to me) or print and fax (205-934-3100) to me. Once I hear back from anyone, if there are no further major comments, I will send to the Publications subcommittee, and then make changes in response to Publication Subcomm Reviewer comments, and then finally send for NICHD Clearance before submission.

Sincerely,  
Ambal

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**From:** Namasivayam Ambalavanan [NAmbalavanan@peds.uab.edu]  
**Sent:** Friday, July 05, 2013 11:35 AM  
**To:** Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Shankaran, Seetha; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Fourth draft of July 5, 2013

Dear All,

Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

- 1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
- 2) Some clarifications of methods and explanations in Discussion.
- 3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,  
Ambal

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**From:** Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]  
**Sent:** Tuesday, March 05, 2013 12:54 PM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,

Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx) - some comments may need additional analysis ( Lisa, would you look over the comments of Abhik Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Thursday, February 21, 2013 10:37 AM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : first draft of Feb21, 2013  
**Importance:** High

Dear All,

Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)

Thank you for all your help,  
Best regards,  
Ambal

Namasivayam Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology  
University of Alabama at Birmingham

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Birmingham, AL 35249-7335  
**Tel Office** (205) 934 4680 **Lab** (205) 934 0751 or 996 5419  
**Fax Office** (205) 934-3100 **Lab** (205) 996 2333  
**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Wednesday, February 02, 2011 10:06 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,  
Our PAS abstract on PaCO<sub>2</sub> in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,  
Thank you for all your help,  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Mon 11/8/2010 5:40 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,  
Attached is the abstract on PaCO<sub>2</sub> SUPPORT abstract for NICHD clearance.  
Thank you,  
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO<sub>2</sub> variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO<sub>2</sub> in the CPAP arm from about 33 to 34. The Max PaCO<sub>2</sub> was about the same in all groups)

Thanks,  
Ambal

N. Ambalavanan MD  
Professor, Division of Neonatology  
Departments of Pediatrics, Cell Biology, and Pathology

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619 South 19th Street  
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Tel Office (205) 934 4680 Lab (205) 934 0751 or 996 5419  
Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Sun 10/31/2010 6:25 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.

Ambal  
(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

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**From:** Namasivayam Ambalavanan  
**Sent:** Sat 10/30/2010 8:15 PM  
**To:** Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as

1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,  
Ambal

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**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Sat 10/30/2010 4:59 PM  
**To:** Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

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**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Saturday, October 30, 2010 10:18 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.  
Best Michele

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Fri 10/29/2010 5:28 PM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO<sub>2</sub> in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Namasivayam Ambalavanan  
**Sent:** Saturday, October 23, 2010 7:16 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO<sub>2</sub> (using highest FiO<sub>2</sub> on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?  
Ambal

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**From:** Namasivayam Ambalavanan  
**Sent:** Fri 10/22/2010 8:58 PM  
**To:** Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO<sub>2</sub> (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO<sub>2</sub> and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO<sub>2</sub>. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident

that higher PaCO<sub>2</sub> were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.  
Ambal

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**From:** Michael Cotten [<mailto:cotte010@mc.duke.edu>]  
**Sent:** Fri 10/22/2010 7:57 PM  
**To:** Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon  
**Subject:** Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co<sub>2</sub>? Some babies are easily hyperventilatable, and sometimes practitioners allow co<sub>2</sub> to be high on min settings,,,and those kids are probably way different than kids on high settings or hfv who remain hypercarbic,,,

Mc

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**From:** "Namasivayam Ambalavanan" [[NAmbalavanan@peds.uab.edu](mailto:NAmbalavanan@peds.uab.edu)]  
**Sent:** 10/22/2010 03:59 PM EST  
**To:** "Wrage, Lisa Ann" <[wrage@rti.org](mailto:wrage@rti.org)>; <[ambal@uab.edu](mailto:ambal@uab.edu)>  
**Cc:** "Das, Abhik" <[adas@rti.org](mailto:adas@rti.org)>; "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)>; "Wally Carlo, M.D." <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; "Kennedy, Kathleen A" <[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)>; "Laptook, Abbot" <[ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org)>; "Higgins, Rosemary (NIH/NICHD)" [[E](mailto:E)] <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>; <[Michele.Walsh@UHHospitals.org](mailto:Michele.Walsh@UHHospitals.org)>; Michael Cotten; "Laughon, Matthew M" <[matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu)>  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO<sub>2</sub> (especially higher PaCO<sub>2</sub> and fluctuating PaCO<sub>2</sub>) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO<sub>2</sub> is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO<sub>2</sub>, minimal PaCO<sub>2</sub>, time-weighted PaCO<sub>2</sub>, and SD of PaCO<sub>2</sub> as independent continuous variables with actual time-weighted PaO<sub>2</sub> (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if

<3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO2 for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO2 variables with outcome, after adjustment for the other variables. We probably do not need PaCO2 values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO2 and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO2 terms (Abhik – any suggestions?). Also, we had discussed that if the relationship of PaCO2 to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO2 category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO2 categories and the numbers in each CO2 category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 22, 2010 2:48 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO2 variables of interest and 4 outcomes of interest (=potentially 5x4

models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Wednesday, October 20, 2010 10:58 AM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.  
Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Wed 10/20/2010 9:42 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO2, Wally and Marie did decide to cap the amount of time that on CO2 level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.

Thanks.

Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis butI think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

**From:** Gantz, Marie <[mgantz@rti.org](mailto:mgantz@rti.org)>  
**Sent:** Tuesday, October 19, 2010 7:29 PM  
**To:** Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; Finer, Neil <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>

Cc: Das, Abhik <adas@rti.org>; Wrage, Lisa Ann <wrage@rti.org>  
Subject: RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO2 for his paper. When we look at the actual times of CO2 data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO2 measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between CO2 measurements:

50th 8.5  
75th 12  
90th 21  
95th 25.5  
99th 80  
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

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**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 15, 2010 2:56 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
Thank you for the email.

- 1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.
  - 2) I think PROM>24h is ok
  - 3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.
  - 4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.
- Ambal

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**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 15, 2010 1:46 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted C02 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95<sup>th</sup> %ile is 25.1 hours and the 99<sup>th</sup>%ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,  
Lisa

---

**From:** Wrage, Lisa Ann  
**Sent:** Tuesday, October 05, 2010 2:45 PM  
**To:** 'Namasivayam Ambalavanan'; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.

Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 2:38 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
My answers (>>) are below your questions (\*\*)

Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 12:36 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Thank you, this is helpful, I have a few more questions (see \*\* below).  
Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 12:42 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
(Abhik/Wally/Marie -- your comments are also welcome)  
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

**\*\*Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.**

**>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices**

- 2) For Aim (1): determine the association of PaCO<sub>2</sub> in the first 2 weeks with outcomes, we will use PaCO<sub>2</sub> as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes, antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

**\*\*Could you please clarify how you like to summarize PaCO<sub>2</sub> over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?**

**>> I think max, min, time-weighted, and standard deviation should be ok.**

- 3) For Aims (2) and (3), to determine the association of high/low PaCO<sub>2</sub> with outcomes, we will divide infants into quartiles based on their maximum PCO<sub>2</sub> and their minimum PCO<sub>2</sub> over the first two weeks. The infants in the highest quartile of max PCO<sub>2</sub> are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO<sub>2</sub> will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO<sub>2</sub> and minimum PCO<sub>2</sub>. The outcomes will be assessed in the low and high SpO<sub>2</sub> groups in relation to PaCO<sub>2</sub> status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

**\*\*So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO<sub>2</sub>), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators].**

**Hypocapnic (in lower quartile of min PCO<sub>2</sub>), >> Yes. As above, I think we should have hypocapnia only, not fluctuators.**

**Fluctuators (in both upper quartile of max PCO<sub>2</sub> lower quartile of min PCO<sub>2</sub>) >> Yes.**

**Normocapnic (in middle two quartiles of max PCO<sub>2</sub> AND min PCO<sub>2</sub>)**

**To define Max PCO<sub>2</sub> and Min PCO<sub>2</sub> do you simply want me to use the maximum and minimum value of all values of PCO<sub>2</sub> for each infant using PCO<sub>2</sub> recorded during the 1<sup>st</sup> two weeks on the SUPP05 form?**

**>> Yes**

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO<sub>2</sub>, minPCO<sub>2</sub>, time-weighted PCO<sub>2</sub>, and SD of PCO<sub>2</sub> as independent continuous variables with SUPPORT group assignment

**\*\*OK.**

**>>>Great!**

Thanks,

Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 10:32 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc.", could you please provide a complete list?

Thank-you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 01, 2010 11:14 AM  
**To:** Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Hi Lisa, Marie,

What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?

Ambal

N. Ambalavanan MD

Division of Neonatology,

Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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---

**From:** Das, Abhik [<mailto:adas@rti.org>]

**Sent:** Tuesday, September 21, 2010 3:55 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; [ambal@uab.edu](mailto:ambal@uab.edu)

**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie

**Subject:** RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

**Sent:** Tuesday, September 21, 2010 11:15 AM

**To:** Ambal ([ambal@uab.edu](mailto:ambal@uab.edu))

**Cc:** Wally Carlo, M.D.; Das, Abhik

**Subject:** PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

**For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.**

November 8, 2010– Final abstracts to NICHD for clearance  
Mid-November– PAS deadline  
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks  
Rose

Rosemary D. Higgins, MD  
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**Title:**

**Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

**Authors:**

Namasivayam Ambalavanan MD<sup>1</sup>; Waldemar A. Carlo MD<sup>1</sup>; Lisa A. Wrage MPH<sup>2</sup>; Abhik Das PhD<sup>3</sup>; Matthew Laughon MD MPH<sup>4</sup>; C. Michael Cotten MD MHS<sup>5</sup>; Kathleen A. Kennedy MD MPH<sup>6</sup>; Abbot R. Laptook MD<sup>7</sup>; Seetha Shankaran MD<sup>8</sup>; Michele C. Walsh MD MS<sup>9</sup>; Rosemary D. Higgins MD<sup>10</sup>; For the SUPPORT Study Group of the NICHD Neonatal Research Network

**Author Affiliations:**

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**Short Title: PaCO<sub>2</sub> and IVH**

**Abbreviations:** BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

**Keywords:** Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

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**Funding source:** Supported by grants from the National Institute of Child Health and Human Development and the Department of Health and Human Services with co-funding from the National Heart, Lung, and Blood Institute (NHLBI) (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27871, U10 HD27880, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, U10 HD53124) and from the National Institutes of Health (M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, M01 RR125, M01 RR633,

M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

**Conflicts of interest:** The authors have no conflicts of interest relevant to this article to disclose.

**Word count:** abstract: 250; text of manuscript: 3075 (Introduction, Methods, Results, and Discussion).

**What's known on this subject:** Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

**What this study adds:** Higher  $\text{PaCO}_2$  and greater fluctuation in  $\text{PaCO}_2$  were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of  $\text{PaCO}_2$  with  $\text{FiO}_2$  and days of ventilation support higher maximum  $\text{PaCO}_2$  as a marker of illness severity in extremely premature infants

**ABSTRACT:**

**Objective:** To determine the association of PaCO<sub>2</sub> with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO<sub>2</sub> targets of 85-89% vs 91-95%) and ventilation strategies. Five PaCO<sub>2</sub> variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO<sub>2</sub>], hypocapnic [lowest quartile of Min PaCO<sub>2</sub>], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO<sub>2</sub>]). Adjusted and unadjusted analyses compared PaCO<sub>2</sub> variables for infants with and without sIVH, BPD, and NDI (+/- death). **Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all p <0.0001). A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> (r<sub>s</sub>0.55, p<0.0001) & ventilator days (r<sub>s</sub>0.61, p<0.0001). **Conclusions:** Higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). Correlation of PaCO<sub>2</sub> with FiO<sub>2</sub> and ventilator days supports higher Max PaCO<sub>2</sub> as a marker of illness severity.

(Abstract Word Count = 250)

## MANUSCRIPT TEXT

### INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are associated with and may possibly contribute to outcomes of prematurity such as intraventricular hemorrhage (IVH)<sup>1</sup>, periventricular leukomalacia (PVL)<sup>2, 3</sup>, bronchopulmonary dysplasia (BPD)<sup>4</sup>, and subsequent neurodevelopmental impairment (NDI)<sup>5</sup>. Increased  $\text{PaCO}_2$  increases cerebral blood flow,<sup>6-8</sup> while decreased  $\text{PaCO}_2$  reduces cerebral blood flow and electrical activity, while increasing cerebral fractional oxygen extraction.<sup>9</sup> We have previously shown that both high and low  $\text{PaCO}_2$  levels and wide fluctuations in  $\text{PaCO}_2$  are associated with a higher risk of severe IVH (sIVH; IVH Grades III or IV).<sup>1</sup> Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.<sup>2, 3, 10</sup>

Cerebral blood flow decreases slightly with increased oxygenation<sup>8</sup> but the interactions between  $\text{PaCO}_2$  and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher  $\text{PaCO}_2$ <sup>4, 11, 12</sup> as well as a lower oxygen saturation ( $\text{SpO}_2$ ) target,<sup>13</sup> permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher  $\text{PaCO}_2$  (permissive hypercapnia) as well as a lower  $\text{PaO}_2$  (targeting a lower  $\text{SpO}_2$  range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation and compared outcomes in infants randomly assigned to  $\text{SpO}_2$  targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a  $\text{PaCO}_2 > 65$  mm Hg permitted intubation, while a  $\text{PaCO}_2 < 65$  mm Hg with a  $\text{pH} > 7.20$  was a mandatory extubation criterion) or intubation and surfactant within 1 hour after birth (a

PaCO<sub>2</sub><50 mm Hg with a pH>7.30 was a mandatory extubation criterion).<sup>13, 14</sup> Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP (higher PaCO<sub>2</sub> target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by postnatal day 7. In the lower SpO<sub>2</sub> target group, death occurred more frequently (19.9 vs. 16.2%; p= 0.04) while severe retinopathy among survivors occurred less often (8.6 vs. 17.9%; p<0.001), without significant differences in other outcomes although a trend for reduced BPD (physiological definition)<sup>15, 16</sup> was noted in the lower SpO<sub>2</sub> target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).<sup>13</sup> However, no significant differences in the composite outcome of death or NDI were noted among infants in any of the treatment groups.<sup>17</sup>

It is possible that clinical outcomes that are not significantly different by SpO<sub>2</sub> target groups might be different when the combination of PaCO<sub>2</sub> and SpO<sub>2</sub> is analyzed. We hypothesized that both extremes of PaCO<sub>2</sub> would be associated with severe IVH, and that effect modification of SpO<sub>2</sub> will be observed, with hypercapnia associated with sIVH in the low but not high SpO<sub>2</sub> group. We also hypothesized that BPD would be lower in infants with hypercapnia and low SpO<sub>2</sub>, and that higher PaCO<sub>2</sub> will be associated with a higher risk of NDI.

## **PATIENTS AND METHODS**

### **Patient characteristics:**

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.<sup>13, 14</sup> Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical

outcomes, and treatment. The characteristics of this population<sup>13</sup> and of the follow-up cohort<sup>17</sup> have been previously reported.

### **PaCO<sub>2</sub> variables**

Five PaCO<sub>2</sub> variables were defined for this observational study, using routine blood gas measurements not governed by study protocol. Data were collected on all PaCO<sub>2</sub> from blood gases done at 3 daily time points closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max PaCO<sub>2</sub>), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO<sub>2</sub> was calculated as described previously:<sup>1</sup> briefly, the sum of all PaCO<sub>2</sub> values multiplied by the corresponding time interval (from previous blood gas) was divided by the overall time period. Time between blood gases was capped at 24 hours (~5% of all measurements) so any one blood gas represents no more than a 24 hour period. The median (mean; 5<sup>th</sup>-95<sup>th</sup> centiles) number of blood gases per infant was 2 (2, 1-3) on study day 1, 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO<sub>2</sub> over days 1-14 into quartiles. Infants with minimum PaCO<sub>2</sub> in the lowest quartile who were not also in the highest quartile of maximum PaCO<sub>2</sub> were then categorized as 'hypocapnic'. Infants with maximum PaCO<sub>2</sub> levels in the highest quartile who were not also in the lowest quartile of minimum PaCO<sub>2</sub> level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO<sub>2</sub> and the highest quartile of maximum PaCO<sub>2</sub> were categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO<sub>2</sub> level fall in quartiles 2-4 and maximum PaCO<sub>2</sub> levels fall in quartiles 1-3 were categorized as 'normocapnic'.

### **Other variables**

Maternal hypertension was defined as pregnancy induced hypertension (PIH). Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum  $\text{FiO}_2$  was defined as the maximum of  $\text{FiO}_2$  at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as  $\text{FiO}_2 > 0.4$  and mechanical ventilation for 8+ hours in the 1<sup>st</sup> 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),<sup>18</sup> and BPD was defined using the physiologic definition at 36 w PMA.<sup>15, 16</sup> Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.<sup>17</sup>

#### **Statistical Analysis**

The  $\text{PaCO}_2$  and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the  $\text{PaCO}_2$  and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance ( $p < .05$ ) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis-generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the maximum  $\text{PaCO}_2$ , the 4 level  $\text{PaCO}_2$  categorical variable, as well as time-weighted  $\text{PaCO}_2$  were obtained using generalized estimating equation (GEE) models for binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for multiple births randomized to the same

treatment arm in SUPPORT. Variables included in models along with the PaCO<sub>2</sub> variable were: birth weight, GA group, gender, race, prenatal steroids, PIH, premature rupture of membranes, and center. SUPPORT treatment group variables (High/Low SpO<sub>2</sub>; CPAP/ventilator) were also included in models that contained maximum PaCO<sub>2</sub> and the 4 level PaCO<sub>2</sub> variable. Interactions of these PaCO<sub>2</sub> and treatment group variables were also included to assess if the effect of PaCO<sub>2</sub> varied by treatment group. A variable for actual median SpO<sub>2</sub> in the first 14 days was included in the model that contained time-weighted PaCO<sub>2</sub>. The interaction of these two variables was included to assess if the effect of time-weighted PaCO<sub>2</sub> varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

## RESULTS

### Adjusted analysis for Severe IVH/Death (Table 1):

Maximum PaCO<sub>2</sub> was significantly associated with higher odds of sIVH/death (OR 1.39, 95% CI 1.27-1.53 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < .0001$ ). No interaction was found between PaCO<sub>2</sub> category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (High or Low SpO<sub>2</sub>), but the interaction term for time-weighted PaCO<sub>2</sub> and median SpO<sub>2</sub> in the first 14 days was significant ( $p < 0.05$ ), with a higher OR associated with a lower median SpO<sub>2</sub> (OR of 1.6 for median SpO<sub>2</sub> of 91, 1.44 for SpO<sub>2</sub> of 92, 1.30 for SpO<sub>2</sub> of 93, 1.18 for SpO<sub>2</sub> of 94) indicating that a higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

Other variables associated ( $p < 0.05$ ) with sIVH/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for BPD/Death (**Table 2**):

Maximum PaCO<sub>2</sub> (OR 1.57, 95% CI 1.41-1.75 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 2.41, 95% CI 1.89-3.09 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of BPD/death. The interaction term between PaCO<sub>2</sub> category and treatment group (High or Low SpO<sub>2</sub>) was significant for fluctuators ( $p = 0.006$ ), with the OR for fluctuators in the High SpO<sub>2</sub> group being 7.4, as compared to 1.18 for the low SpO<sub>2</sub> group.

Other variables associated ( $p < 0.05$ ) with BPD/death included: lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (**Table 3**):

Maximum PaCO<sub>2</sub> (OR 1.38, 95% CI 1.25-1.52 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) and time-weighted PaCO<sub>2</sub> (OR 1.44, 95% CI 1.09-1.90 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) were associated with higher odds of NDI/death. No significant interactions were noted between PaCO<sub>2</sub> category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (reference group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with NDI/death included: lower birth weight and gestational age, male gender, absence of PIH, and center.

Adjusted analysis for Death before discharge (**Table 4**):

Maximum PaCO<sub>2</sub> (OR 1.36, 95% CI 1.22-1.51 for an increase in maximum PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ) was associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (reference

group) or hypocapnic infants. Other variables associated ( $p < 0.05$ ) with death before discharge included: lower birth weight, male gender, absence of PIH, and center.

As higher maximum PaCO<sub>2</sub> may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher maximum FiO<sub>2</sub>, days of mechanical ventilation, and severe illness), correlations of maximum PaCO<sub>2</sub> with maximum FiO<sub>2</sub>, days of ventilation, and severe illness (as previously defined) were calculated. Maximum PaCO<sub>2</sub> was positively correlated with both maximum FiO<sub>2</sub> (Spearman correlation coefficient = 0.55,  $p < 0.0001$ ) and days of ventilation (Spearman correlation coefficient = 0.61,  $p < 0.0001$ ). There was also a significant difference in PaCO<sub>2</sub> level by infants defined as having severe illness (median maximum PaCO<sub>2</sub>=78) vs. infants having no severe illness (median maximum PaCO<sub>2</sub>=61),  $p < 0.0001$ .

#### Unadjusted Results (Supplemental Tables 1-4):

All PaCO<sub>2</sub> variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in PaCO<sub>2</sub> as compared to those without sIVH. Maximum PaCO<sub>2</sub> demonstrated the largest magnitude of separation, with a difference of almost 10 mm Hg in the mean and median maximum PaCO<sub>2</sub> between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted PaCO<sub>2</sub> were statistically highly significant ( $p < 0.0001$ ) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted

PaCO<sub>2</sub> compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

## DISCUSSION

We found that extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO<sub>2</sub> in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO<sub>2</sub>, days of ventilation, and severe illness). A higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower. Greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> and not in the low SpO<sub>2</sub> group.

Our study has the limitation that infants in the SUPPORT trial<sup>13, 14</sup> were not primarily randomized to different specific PaCO<sub>2</sub> ranges as in the randomized trials of permissive hypercapnia<sup>4, 12, 19</sup> but to interventions (Early CPAP vs. intubation/surfactant) with different PaCO<sub>2</sub> goals. Data on corresponding ventilator settings and oxygenation index are not available to determine if reduction of PaCO<sub>2</sub> using higher ventilator settings was associated with better outcome in the SUPPORT trial. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Eighteen to 22 month follow-up was achieved in most infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups, probably because randomization in this trial most likely led to a similar range of PaCO<sub>2</sub> in both SpO<sub>2</sub> groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in

PaCO<sub>2</sub> secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.<sup>14</sup> An additional strength of our study is that we evaluated both interaction with actual saturation and treatment group (high or low SpO<sub>2</sub> target), in order to distinguish illness severity and effects of treatment group allocation (e.g. higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the actual SpO<sub>2</sub> was lower, but there was no interaction with treatment group).

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO<sub>2</sub> levels and wide fluctuations in PaCO<sub>2</sub> are associated with an increased risk of sIVH.<sup>1</sup> The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO<sub>2</sub> were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO<sub>2</sub>. As maximum PaCO<sub>2</sub> was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO<sub>2</sub> had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average PaCO<sub>2</sub> in combination with a lower SpO<sub>2</sub> being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) PaCO<sub>2</sub> even in infants without severe IVH was  $\geq 48$  mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the “permissive hypercapnia” range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.<sup>12</sup> Our data indicate clinical practices in academic centers have evolved to maintain PaCO<sub>2</sub> in the permissive hypercapnia

range. However, as the maximum PaCO<sub>2</sub> exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO<sub>2</sub> within this narrow range is difficult.

A higher maximum and time-weighted PaCO<sub>2</sub> and a greater magnitude of fluctuation in PaCO<sub>2</sub> were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher PaCO<sub>2</sub> rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO<sub>2</sub> elimination for a given minute ventilation, due to a higher alveolar CO<sub>2</sub> (P<sub>A</sub>CO<sub>2</sub>). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing PaCO<sub>2</sub>, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in ventilator weaning. However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.<sup>4, 11, 12, 19</sup> In the largest randomized trial of permissive hypercapnia to date, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group (p<0.01).<sup>4</sup> An interesting finding in the present study was that greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> but not in the low SpO<sub>2</sub> group. It is speculated that higher oxygen exposure in the high SpO<sub>2</sub> group may interact with volutrauma/atelectrauma associated with fluctuating PaCO<sub>2</sub> possibly increasing the risk for BPD/death.

Maximum PaCO<sub>2</sub> was also significantly associated with higher NDI/death, confirming our previous single-center study.<sup>5</sup> This association may be secondary to maximum PaCO<sub>2</sub> being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.<sup>20</sup> Alterations in PaCO<sub>2</sub> may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO<sub>2</sub><sup>6-8</sup> may result in sIVH<sup>1</sup> and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO<sub>2</sub><sup>9</sup> may lower white matter perfusion and result in periventricular leukomalacia (PVL).<sup>2, 3, 10</sup> Brain injury associated with extremes of PaCO<sub>2</sub> may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.<sup>21, 22</sup>

In conclusion, our work demonstrates that maximum PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, maximum PaCO<sub>2</sub> may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.

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**Table 1: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of severe IVH/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.39 (1.27-1.53)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.11 (0.73-1.67)	0.63
<b>Hypercapnic</b>	2.60 (1.77-3.82)	<0.0001
<b>Fluctuator</b>	2.81 (1.68-4.72)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub>**</b> <b>(per 10 mm Hg)</b>		
<b>Median SpO<sub>2</sub>=91</b>	1.60 (1.17-2.17)	0.003
<b>Median SpO<sub>2</sub>=94</b>	1.18 (0.85-1.62)	0.32

\*\* interaction term for time-weighted PaCO<sub>2</sub> x Median SpO<sub>2</sub> in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted PaCO<sub>2</sub> depended on level of Median SpO<sub>2</sub>.

**Table 2:** Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of BPD/death

PaCO <sub>2</sub> Variable	Adjusted Odds Ratio (95% CI)	p-value
<b>Max PaCO<sub>2</sub></b> (per 10 mm Hg)	1.57 (1.41-1.75)	<0.0001
<b>PaCO<sub>2</sub> Category: <u>High SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	0.73 (0.46-1.16)	0.18
<b>Hypercapnic</b>	2.54 (1.41-4.60)	0.002
<b>Fluctuator</b>	7.4 (2.6-21.0)	0.0002
<b>Normocapnic</b>	REFERENCE	-
<b><u>Low SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	1.01 (0.63-1.63)	0.96
<b>Hypercapnic</b>	3.38 (1.93-5.93)	<0.0001
<b>Fluctuator</b>	1.18 (0.51-2.70)	0.70
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> (per 10 mm Hg)	2.41 (1.89-3.09)	<0.0001

\*\* interaction term for PaCO<sub>2</sub> category x treatment group (High or Low SpO<sub>2</sub>) was significant for Fluctuators

**Table 3: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of NDI/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.38 (1.25-1.52)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.03 (0.69-1.53)	0.90
<b>Hypercapnic</b>	2.69 (1.82-3.96)	<0.0001
<b>Fluctuator</b>	3.07 (1.84-5.12)	<0.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.44 (1.09-1.90)	0.009

**Table 4: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of death before discharge**

<b>PaCO<sub>2</sub> Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.36 (1.22-1.51)	<0.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	0.90 (0.54-1.50)	0.07
<b>Hypercapnic</b>	2.47 (1.61-3.77)	<0.0001
<b>Fluctuator</b>	1.88 (1.03-3.43)	0.04
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.28 (0.94-1.74)	0.12

## **Supplemental Tables**

**Supplemental Tables:**

**Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH**

<b>Characteristic</b>		<b>Severe IVH (N=164)</b>	<b>No Severe IVH (N=1106)</b>	<b>p-value<sup>1</sup></b>	<b>Death or Severe IVH (N=335)</b>	<b>No Death or Severe IVH (N=979)</b>	<b>p-value<sup>1</sup></b>
<b>PaCO<sub>2</sub>, minimum level</b>	#	163	1098		325	971	
	Mean (SD)	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	Median, IQR	32 (27-37)	34 (29-38)	0.005	33 (28-38)	34 (30-38)	0.69
<b>PaCO<sub>2</sub>, maximum level</b>	#	163	1098		325	971	
	Mean (SD)	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	Median, IQR	75 (63-85)	65.5 (55-75)	<0.0001	76 (65-88)	64 (54-74)	<0.0001
<b>PaCO<sub>2</sub>, standard deviation</b>	#	163	1077		314	951	
	Mean (SD)	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	Median, IQR	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<0.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<0.0001
<b>PaCO<sub>2</sub>, time-weighted</b>	#	163	1098		325	971	
	Mean (SD)	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	Median, IQR	49.4 (45.8-54.2)	48.6 (43.6-52.9)	0.009	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<0.0001
<b>PaCO<sub>2</sub> category:</b>	#	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
	# (%)			<0.0001			<0.0001
Hypocapnic		30 (18.4)	205 (18.7)		48 (14.8)	189 (19.5)	
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65(39.9)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	0.13	166 (49.6)	496 (50.7)	0.73
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	164	1106		335	979	
	High O <sub>2</sub> , # (%)	81 (49.4)	559 (50.5)	0.78	156 (46.6)	505 (51.6)	0.11
Median SpO <sub>2</sub> DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	0.03	750 (640-881)	850 (710-990)	<0.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	0.08	197 (58.8)	514 (52.5)	0.046
Race:	# (%)						
NH Black		55 (33.5)	421 (38.1)	0.016	112 (33.4)	376 (38.4)	0.09
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	0.26	112 (33.4)	376 (38.4)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	0.12	133 (39.7)	387 (39.5)	0.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	0.03	21 (6.6)	110 (12.0)	0.008
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	0.006	97 (30.4)	336 (34.9)	0.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	0.84	325 (97.3)	938 (95.8)	0.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	0.022	120 (35.9)	200 (20.4)	<0.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	0.04	29 (8.7)	29 (3.0)	<0.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	0.47	117 (37.9)	384 (39.2)	0.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	0.69	108 (32.2)	325 (33.2)	0.74

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p-value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	441	659		639	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	0.015	33 (29-38)	34 (30-38)	0.25
PaCO <sub>2</sub> , maximum level	#	441	659		639	659	
	Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<0.0001	73 (65-85)	60 (50-69)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	438	642		625	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<0.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	441	659		639	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<0.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<0.0001
PaCO <sub>2</sub> category:	#	441	659		639	659	
Hypocapnic	# (%)	78 (17.7)	138 (20.9)	<0.0001	100 (15.7)	138 (20.9)	<0.0001
Hypercapnic		101 (22.9)	59 (9.0)		170 (26.6)	59 (9)	
Fluctuator		48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)	
Normocapnic		214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)	
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, (%)	223 (50.4)	346 (52)	0.62	317 (48.8)	346 (52.0)	0.25

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	442	666		650	666	
	High O <sub>2</sub> , # (%)	237 (53.6)	331 (49.7)	0.20	331 (50.9)	331 (49.7)	0.66
Median SpO <sub>2</sub> DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<0.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<0.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650-870)	900 (770-1020)	<0.0001	740 (643-870)	900 (770-1020)	<0.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	0.04	375 (57.7)	337 (50.6)	0.01
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	0.013	221 (34)	268 (40.2)	0.02
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	157 (35.5)	268 (40.2)	0.11	221 (34)	268 (40.2)	0.02
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	200 (45.3)	237 (35.6)	0.001	284 (43.7)	237 (35.6)	0.003
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	0.18	68 (11.1)	63 (10.1)	0.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	0.22
Prenatal steroids	#	442	666		649	666	

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death BPD (N=650)	or No Death or BPD (N=666)	p- value <sup>1</sup>
	Yes, # (%)	427 (96.6)	636 (95.5)	0.36	629 (96.9)	636 (95.5)	0.18
<b>1 minute Apgar &lt; 3</b>	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<0.0001	207 (31.9)	114 (17.1)	<0.0001
<b>5 minute Apgar &lt; 3</b>	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	0.11	41 (6.3)	17 (2.6)	0.001
<b>Prophylactic indomethacin</b>	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	0.75	240 (38.5)	261 (39.2)	0.79
<b>Vaginal delivery</b>	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240 (36.0)	0.004	193 (29.7)	240 (36.0)	0.01

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	0.001	33 (28-38)	33 (30-38)	0.95
PaCO <sub>2</sub> , maximum level	#	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<0.0001	76 (66-88)	64 (54-74)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<0.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	0.0014	51.7 (47.1-56)	48 (42.8-52.3)	<0.0001
PaCO <sub>2</sub> category:	#	98	872		346	872	
Hypocapnic	# (%)	22 (22.5)	171 (19.6)	<0.0001	51 (14.7)	171 (19.6)	<0.0001
Hypercapnic		25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)		135 (39.0)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	98	878		356	878	
	High O <sub>2</sub> , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
Median SpO <sub>2</sub> DOL 1-14	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92- 94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<0.0001
Birth Weight (g)	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643- 914)	850 (710- 995)	<0.0001	734 (621- 870)	850 (710- 995)	<0.0001
Gender	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	0.01
Race:	# (%)						
NH Black		37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
NH White		37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other		3 (3.1)	30 (3.4)		14 (3.9)	30 (3.4)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
HTN, pregnancy induced	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
Rupture of membranes > 24 hours prior to birth	#	97	863		341	863	
	Yes, # (%)	26 ( 26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
Prenatal steroids	#	98	878		355	878	
	Yes, # (%)	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
1 minute Apgar < 3	#	98	877		355	877	
	Yes, # (%)	36 (36.7)	181 (20.6)	0.0003	130 (36.6)	181 (20.6)	<0.0001
5 minute Apgar < 3	#	98	878		356	878	
	Yes, # (%)	7 (7.1)	27 (3.1)	0.04	29 (8.2)	27 (3.1)	0.0001
Prophylactic indomethacin	#	98	878		330	878	
	Yes, # (%)	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
Vaginal delivery	#	98	878		356	878	
	Yes, # (%)	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	0.026
PaCO <sub>2</sub> , maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<0.0001
PaCO <sub>2</sub> , standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<0.0001
PaCO <sub>2</sub> , time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<0.0001
PaCO <sub>2</sub> category:	#	227	991	
Hypocapnic	# (%)	26 (11.5)	196 (19.8)	<0.0001
Hypercapnic		82 (36.1)	140 (14.1)	
Fluctuator		29 (12.8)	64 (6.5)	
Normocapnic		90 (39.7)	591 (59.6)	
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	237	997	
	High O <sub>2</sub> , # (%)	107 (45.2)	515 (51.7)	0.07
Median SpO <sub>2</sub> DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<0.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<0.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	0.026
Race:	# (%)			
NH Black		77(32.5)	381 (38.2)	0.26
NH White		96 (40.5)	397 (39.8)	
Hispanic		53 (22.4)	186 (18.7)	
Other		11 (4.6)	33 (3.3)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	Yes, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<0.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<0.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

## References

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NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title of manuscript Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure,  
First author Namasivayam Ambalavanan MD

A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

B. I have read and given final approval of the submitted manuscript.

C. To qualify for authorship, you must check at least 1 box for each of the 3 categories of contributions listed below.

I have made substantial contributions to the intellectual content of the paper as described below.

1. (check at least 1 of the 3 below)

- conception and design
- acquisition of data
- analysis and interpretation of data

2. (check at least 1 of 2 below)

- drafting of the manuscript
- critical revision of the manuscript for important intellectual content

3. (check at least 1 below)

- statistical analysis
- obtaining funding
- administrative, technical, or material support
- supervision
- no additional contributions
- other (specify)
- or are disclosed in an attachment.

Your Signature \_\_\_\_\_ Date Signed \_\_\_\_\_

## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, August 01, 2013 2:41 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]  
**Subject:** FW: article about SUPPORT issue

FYI from today

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Johnson, Karen (Pediatrics) [<mailto:karen-johnson@uiowa.edu>]  
**Sent:** Thursday, August 01, 2013 12:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward (Pediatrics)  
**Subject:** article about SUPPORT issue

Rose,  
I get this online "Journal of Clinical Research Best Practices". I thought this was a pretty good article in this month's issue:  
[http://www.firstclinical.com/journal/2013/1308\\_SUPPORT.pdf](http://www.firstclinical.com/journal/2013/1308_SUPPORT.pdf)

## **Karen**

---

Karen Johnson, RN  
Neonatal Research Network Coordinator  
Pediatrics, Neonatology  
8900 JPP  
University of Iowa Children's Hospital  
Iowa City, Iowa 52242  
(319) 356-2924  
pager (319) 356-1616, ask for pager (b)(6)

"Do not go where the path may lead, go instead where there is no path and leave a trail."

---

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---

**From:** Bell, Edward (Pediatrics)  
**To:** Johnson, Karen (Pediatrics)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: article about SUPPORT issue  
**Date:** Thursday, August 01, 2013 1:11:10 PM

---

Nice summary

On Aug 1, 2013, at 11:25 AM, "Johnson, Karen (Pediatrics)" <karen-johnson@uiowa.edu> wrote:

Rose,

I get this online "Journal of Clinical Research Best Practices". I thought this was a pretty good article in this month's issue:

[http://www.firstclinical.com/journal/2013/1308\\_SUPPORT.pdf](http://www.firstclinical.com/journal/2013/1308_SUPPORT.pdf)

## Karen

---

Karen Johnson, RN  
Neonatal Research Network Coordinator  
Pediatrics, Neonatology  
8900 JPP  
University of Iowa Children's Hospital  
Iowa City, Iowa 52242  
(319) 356-2924  
pager (319) 356-1616, ask for pager (b)(6)

"Do not go where the path may lead, go instead where there is no path and leave a trail."

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#); [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#); [Jarman, John \(NIH/NICHD\) \[E\]](#); [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Guttmacher, Alan \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)  
**Date:** Wednesday, July 31, 2013 3:10:42 PM  
**Attachments:** [RE ACTION Request for availability for a meeting to meet with the OIG on a review entitled Office of Human Research Protections Oversight of the SUPPORT Clinical Trial \(OEI-01-13-00420\) - \(Due by noon on 7/31/13\).msg](#)  
[RE OIG inquiry.msg](#)  
[Sign-in Sheet Informational meeting Office of Human Research Protections Oversight of the SUPPORT Clinical Trial \(OEI-01-13-00420\).msg](#)

---

Yvonne and John

I have attached the prior email correspondence regarding the OIG review. I did not receive any FOIA request from the OIG as of yet. I did speak to the OIG folks by telephone on Monday July 29.

Let me know if there is anything needed from me at this point.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**Sent:** Wednesday, July 31, 2013 2:55 PM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

---

**From:** [Maddox, Yvonne \(NIH/NICHD\) \[E\]](#)  
**Sent:** Wednesday, July 31, 2013 2:48 PM  
**To:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#); [Jarman, John \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

This should be handled by OMA, and John Jarman is our contact with OMA, but we would not have most of what's requested. John is aware of this, as we got a heads up email through FIOA. I will email him and the two of us will work out how best to respond.

---

**From:** [Willinger, Marian \(NIH/NICHD\) \[E\]](#)  
**Sent:** Wednesday, July 31, 2013 02:42 PM

**To:** Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]  
**Cc:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** RE: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

I have no experience with this.

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, July 31, 2013 2:37 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Cc:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** RE: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

I, for one, have no idea.

Alan E. Guttmacher, M.D.  
Director  
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
National Institutes of Health  
31 Center Drive  
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url: [nichd.nih.gov](http://nichd.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, July 31, 2013 2:36 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Cc:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** FW: ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

Hi

See the request below – how are these generally handled? Guidance is appreciated.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Brown, Tiffany (NIH/OD) [E]  
**Sent:** Wednesday, July 31, 2013 2:31 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Devaney, Stephanie (NIH/OD) [E]  
**Subject:** ACTION: Provide Data Safety Monitoring Committee (DSMC) information for "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) (Due Date: 8/5/13)

**DUE DATE:** noon on August 5, 2013  
**ACTION:** Please provide the requested DSMC information  
**CONTACT:** Tiffany Brown, OMA, 301.496.2464

The OIG has requested Data Safety Monitoring Committee (DSMC) information for the SUPPORT trial. Specifically,

- All adverse events that occurred in the trial, and the date on which they occurred (in a spreadsheet form if you have it); and
- Copies of all meeting minutes for the DSMC meeting, both the open and closed sessions of those meetings.

Please provide this information by **noon on Monday, August 5<sup>th</sup>**.

Please let me know if you have any questions.

Thanks in advance for your cooperation!

TIFFANY BROWN  
NIH/OD/OMA  
(301) 496-2464 - DIRECT  
(301) 402-0169 - FAX

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** confidential attorney client correspondence  
**Date:** Wednesday, July 31, 2013 12:49:53 PM  
**Importance:** High

---

Hi  
How does this get handled?  
thanks  
Rose  
FYI – OIG call went fine – thanks for your help

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Wednesday, July 31, 2013 12:41 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Requesting Information from RTI re SUPPORT Study (RTI was data coordinator)  
**Importance:** High

FYI!! Not sure if the network needs to weigh in on unblinding the trial!

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

**From:** Kroner, Barbara L.  
**Sent:** Wednesday, July 31, 2013 12:32 PM Eastern Standard Time  
**To:** Das, Abhik  
**Subject:** FW: Requesting Information from RTI re SUPPORT Study (RTI was data coordinator)

Is this your study?

Sent with Good ([www.good.com](http://www.good.com))

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

**From:** Rostkowski, Teresa [[trostkowski@lchb.com](mailto:trostkowski@lchb.com)]  
**Sent:** Wednesday, July 31, 2013 12:28 PM Eastern Standard Time

**To:** Kroner, Barbara L.

**Subject:** Requesting Information from RTI re SUPPORT Study (RTI was data coordinator)

Dear Ms. Kroner,

I was referred to you by the research team in RTI's headquarters because your work with data coordination. Our firm represents a child who was a participant in the SUPPORT study, conducted by NIH and NICHD. RTI was the data coordinator for the study. We requested some information from NIH, and they directed us to RTI, who, they said, has the information. Do you know how we can request the records, or can you direct us to someone you could tell us?

The records we require indicates which arm of the study group (b)(6) was assigned: low or high oxygen; surfactant and/or CPAP.

Thank you for your time and assistance.

Best,

**Lieff  
Cabrer  
Heimann &  
Bernstein**

Attorneys at Law

**Teresa Rostkowski**

Paralegal

[trostkowski@lchb.com](mailto:trostkowski@lchb.com)

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**From:** D'Angio, Carl  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\*Steering Committee Call\*\*\*\*\* Thursday August 1 at 4 PM ET  
**Date:** Tuesday, July 30, 2013 4:58:53 PM

---

Appropos of our other discussion, I have withdrawn my offer to speak at ASBH. I recognize the sensitivity of the issue and would not want to do anything that would add further stress to folks who are already going through very difficult times. Please share this decision as you feel is appropriate.

*Carl*

-----  
Carl T. D'Angio, MD  
Professor of Pediatrics and Medical Humanities & Bioethics  
Director, Neonatal Clinical Research  
Director, Ethics Key Function, URM CTSI  
Division of Neonatology, Golisano Children's Hospital  
University of Rochester Medical Center  
601 Elmwood Avenue, Box 651  
Rochester, NY 14642  
Phone (585) 273-4911, Fax (585) 461-3614  
carl\_dangio@urmc.rochester.edu

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, July 30, 2013 4:13 PM  
**To:** (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara\_stoll@oz.ped.emory.edu; bpointex@iupui.edu; D'Angio, Carl; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Hareesh Kirpalani (KIRPALANI@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); Guillet, Ronnie; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); (kzaterka@rti.org); (mcunningham@rti.org); Jenna Gabrio (jgabrio@rti.org); Phelps, Dale  
**Subject:** \*\*\*\*\*Steering Committee Call\*\*\*\*\* Thursday August 1 at 4 PM ET

Hi

As a follow up to our concurrent research discussion from last week's steering committee meeting, more information is available and a call is needed.

We will meet at 4 pm ET on 8/1/2013. If you or your alternate PI is unable to attend, please ask a designee to attend and inform us.

Dial:  
Within the USA

(b)(6)

or

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Thanks

Rose

**Rosemary D. Higgins, MD**  
**Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network**  
**Pregnancy and Perinatology Branch**  
**NIH**  
**6100 Executive Blvd., Room 4B03**  
**MSC 7510**  
**Bethesda, MD 20892**  
**For overnight delivery use Rockville, MD 20852**  
**301-435-7909**  
**301-496-5575**  
**301-496-3790 (FAX)**  
**[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Brown, Tiffany (NIH/OD) [E]  
**Sent:** Monday, July 29, 2013 2:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]; Hereford, Russell W (OIG/OEI); Buck, Andrea C (OIG/OEI) (Andrea.Buck@oig.hhs.gov); Searcy, Talisha M (OIG/OEI); Galvin, Chris P (OIG/OEI)  
**Cc:** Yates, Kim A (OIG/OEI)  
**Subject:** Sign-in Sheet: Informational meeting: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)

Thank you for your participation in today's meeting!



Info session  
7.29.13 sign-in s...

**TIFFANY BROWN**  
NIH/OD/OMA  
(301) 496-2464 - DIRECT  
(301) 402-0169 - FAX

-----Original Appointment-----

**From:** Brown, Tiffany (NIH/OD) [E]  
**Sent:** Wednesday, July 24, 2013 11:39 AM  
**To:** Brown, Tiffany (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Stein, Meredith (NIH/OD) [E]; (b)(6) (OIG/OEI); (b)(6) (OIG/OEI); (b)(6)@oig.hhs.gov; (b)(6) (OIG/OEI); (b)(6) (OIG/OEI)  
**Cc:** Yates, Kim A (OIG/OEI)  
**Subject:** Informational meeting: "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420)  
**When:** Monday, July 29, 2013 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).  
**Where:** Teleconference - (Dial-in #: (b)(6) Passcode: (b)(6)

**NIH Participants:**

Rosemary Higgins, Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Network, Pregnancy and Perinatology Branch, NICHD  
Stephanie Devaney, Health Scientist Policy Analyst, OD

**OIG Participants:**

(b)(6) Deputy Regional Inspector General (Boston)  
(b)(6) Assistant Inspector General for Evaluations  
(b)(6), Supervisory Program Analyst  
(b)(6), Program Analyst  
(b)(6) Program Analyst

**OIG-NIH INFORMATOINAL MEETING:**

**PARTICIPANT LIST**

***Office of Human Research Protections Oversight of the SUPPORT***

***Clinical Trial***

***(OEI-01-13-00420)***

**July 29, 2013 (1:00PM – 2:00PM)**

<u>NAME</u>	<u>ORGANIZATION</u>	<u>EMAIL</u>	<u>PHONE#</u>
Rosemary Higgins	NIH/NICHD/DER/PPB National Institutes of Health, National Institute of Child Health and Human Development, Division of Extramural Research, Pregnancy and Perinatology Branch, Program Scientist	<a href="mailto:higginsr@mail.nih.gov">higginsr@mail.nih.gov</a>	(301) 435-7909
Stephanie Devaney	NIH/OD Health Scientist Policy Analyst, Office of the Director	<a href="mailto:devaneysa@mail.nih.gov">devaneysa@mail.nih.gov</a>	(301) 402-1994
Meredith Stein	NIH/OD/OMA Office of Management Assessment Director, Division of Outside Review & Liaison and Division of Quality Management	<a href="mailto:steinme@mail.nih.gov">steinme@mail.nih.gov</a>	(301) 402-8482
Tiffany Brown	NIH/OD/OMA Management Analyst <i>Point of Contact for all NIH participants</i>	<a href="mailto:Brownty1@mail.nih.gov">Brownty1@mail.nih.gov</a>	(301) 496-2464
(b)(6)	OIG/OEI Office of Inspector General Office of Evaluations and Inspections Regional Inspector General (boston)	(b)(6)	
	OIG/OEI Deputy Regional Director (Boston)		
	OIG/OEI Assistant Inspector General for Evaluations		
	OIG/OEI Supervisory Program Analyst <i>Analyst-in-Charge</i>		
	GAO/OEI Program Analyst		
	GAO/OEI Program Analyst		

**From:** D'Angio, Carl  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: ASBH presentation  
**Date:** Monday, July 29, 2013 1:53:37 PM

---

Rose,

That's fine. 585-273-4911. Thanks.

*Carl*

---

Carl T. D'Angio, MD  
Professor of Pediatrics and Medical Humanities & Bioethics  
Director, Neonatal Clinical Research  
Director, Ethics Key Function, URM C CTSI  
Division of Neonatology, Golisano Children's Hospital  
University of Rochester Medical Center  
601 Elmwood Avenue, Box 651  
Rochester, NY 14642  
Phone (585) 273-4911, Fax (585) 461-3614  
[carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu)

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, July 29, 2013 1:51 PM  
**To:** D'Angio, Carl  
**Subject:** RE: ASBH presentation

Can I call you after 230 today? What number??

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** D'Angio, Carl [[mailto:Carl\\_Dangio@URMC.Rochester.edu](mailto:Carl_Dangio@URMC.Rochester.edu)]  
**Sent:** Monday, July 29, 2013 1:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** ASBH presentation

Rose,

Would you please call me sometime about the ASBH presentation I discussed with you? Thanks.

*Carl*

---

Carl T. D'Angio, MD  
Professor of Pediatrics and Medical Humanities & Bioethics

**Director, Neonatal Clinical Research**  
**Director, Ethics Key Function, URM CTSI**  
**Division of Neonatology, Golisano Children's Hospital**  
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**601 Elmwood Avenue, Box 651**  
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**Phone (585) 273-4911, Fax (585) 461-3614**  
**[carl\\_dangio@urmc.rochester.edu](mailto:carl_dangio@urmc.rochester.edu)**

**From:** Shankaran, Seetha  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; Michael Cotten, M.D.  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; Higgins, Rosemary (NIH/NICHD) [E]; Matt Laughon; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Shankaran, Seetha  
**Subject:** RE: PaCO2 manuscript : Fourth draft of July 5, 2013  
**Date:** Sunday, July 28, 2013 2:45:53 PM  
**Attachments:** PCO2\_SUPPORT\_July28\_2013[1].docx

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Hi Ambal  
Very comprehensive.  
Hope I am not too late, have added a few comments.  
All the best  
Seetha

---

**From:** Namasivayam Ambalavanan [NAmbalavanan@peds.uab.edu]  
**Sent:** Friday, July 05, 2013 11:35 AM  
**To:** Kennedy, Kathleen A; Michael Cotten, M.D.; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Shankaran, Seetha; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Fourth draft of July 5, 2013

Dear All,  
Here is the much-awaited fourth draft of our manuscript examining PCO2 in SUPPORT. The main changes in this draft are:

- 1) Thanks to much work by Lisa Wrage, the main results are now the adjusted results, and the unadjusted results have been moved to Supplemental Tables
- 2) Some clarifications of methods and explanations in Discussion.
- 3) A few novel results. Eg. an interaction between PCO2 and SpO2 for severe IVH, again suggesting that sicker kids are more likely to have worse outcomes. Again, this is what we'd expect, but I suppose we should not always hope for unexpected findings.

Thanks,  
Ambal

---

**From:** Namasivayam Ambalavanan [mailto:NAmbalavanan@peds.uab.edu]  
**Sent:** Tuesday, March 05, 2013 12:54 PM  
**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten, M.D.; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: PaCO2 manuscript : Second draft of March 5, 2013

Dear All,  
Attached is the second draft of our manuscript (PCO2 SUPPORT March 5 2013.docx). Thank you for all your comments – I have addressed most of them. The main changes are:

- 1) Reduced the 6 tables of unadjusted results into 3 tables (combined BPD and BPD/death into one table, IVH and IVH/death into one table, and NDI and NDI/death into one table).
- 2) Developed a new table of adjusted results
- 3) Boilerplate and author affiliations have been modified (thanks to Stephanie!)

I have combined all the tracked changes into a single multicolored file (ML AL WC AD SWA MG.docx)  
- some comments may need additional analysis ( Lisa, would you look over the comments of Abhik

Das and Marie Gantz and let me know your suggestions on those comments). I will look over any additional suggestions and develop a revised draft for the Publications Subcommittee in a couple of weeks,

Best regards,

Ambal

**From:** Namasivayam Ambalavanan

**Sent:** Thursday, February 21, 2013 10:37 AM

**To:** Kennedy, Kathleen A; Namasivayam Ambalavanan

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: PaCO2 manuscript : first draft of Feb21, 2013

**Importance:** High

Dear All,

Attached is a first draft of a manuscript relating PaCO2 in the SUPPORT study to outcomes (this is based on the abstract that was not accepted for presentation at an earlier PAS). Your comments and suggestions are welcomed. I plan to have a revised draft in a couple of weeks. The manuscript is currently formatted for Pediatrics.

(Stephanie: Would you check the boilerplate and grant acknowledgments?)

Thank you for all your help,

Best regards,

Ambal

Namasivayam Ambalavanan MD

Division of Neonatology,

Professor, Departments of Pediatrics, Pathology, and Cell, Developmental, and Integrative Biology

University of Alabama at Birmingham

**Mailing Address:**

176F Suite 9380, Women and Infants Center

619 South 19th Street

Birmingham, AL 35249-7335

**Tel** Office (205) 934 4680 Lab (205) 934 0751 or 996 5419

**Fax** Office (205) 934-3100 Lab (205) 996 2333

**Email** [ambal@uab.edu](mailto:ambal@uab.edu)

---

**From:** Namasivayam Ambalavanan

**Sent:** Wednesday, February 02, 2011 10:06 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: PaCO2 abstract not accepted.

Dear Colleagues,

Our PAS abstract on PaCO2 in the SUPPORT study was not accepted (both the pink slip and the abstract are attached). Anyway, I will proceed with the manuscript soon,

Thank you for all your help,

Ambal

---

**From:** Namasivayam Ambalavanan

**Sent:** Mon 11/8/2010 5:40 PM

**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann

**Subject:** RE: PAS ABSTRACT: Third Draft (Nov 8, 2010) - For NICHD Clearance

Dear Dr Higgins,  
Attached is the abstract on PaCO2 SUPPORT abstract for NICHD clearance.  
Thank you,  
Ambal

(To other authors: We are at 99.65% of space available. Lisa's analysis indicates that PaCO2 variables did not differ by treatment group, except for a non-clinically significant increase of 1 mm Hg in Minimum PaCO2 in the CPAP arm from about 33 to 34. The Max PaCO2 was about the same in all groups)

Thanks,  
Ambal

N. Ambalavanan MD  
Professor, Division of Neonatology  
Departments of Pediatrics, Cell Biology, and Pathology

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619 South 19th Street  
Birmingham, AL 35249-7335  
Tel Office (205) 934 4680 Lab (205) 934 0751 or 996 5419  
Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

---

**From:** Namasivayam Ambalavanan  
**Sent:** Sun 10/31/2010 6:25 PM  
**To:** Namasivayam Ambalavanan; Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: Second draft (10/31/10)

Thanks to everyone for their useful comments and suggestions. We are now at 99.96% of space available. I have attached the second draft of the abstract.  
Ambal  
(Should we be circulating this to others as well - SUPPORT Subcommittee, etc?)

---

**From:** Namasivayam Ambalavanan  
**Sent:** Sat 10/30/2010 8:15 PM  
**To:** Kennedy, Kathleen A; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: First draft

Thanks to Michele, Kathleen, and Mike for their comments and suggestions. I will circulate a revised draft in a day or two. I am attaching the summary of results.

Regarding Michele's excellent questions:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and severe IVH? another way: is hypercarbia safe?

>> Briefly, I am not sure we will be able to conclusively answer this question using this data set, and think we will have to do a RCT targeting PCO2 ranges with a larger PCO2 spread

between the groups compared to the SAVE trial to answer the question to satisfaction. We do not have information on ventilation variables (other than FiO2 and days on ventilation) in this dataset.

Our initial hypothesis was that BPD and severe IVH may be competing outcomes, both in the sense that infants with severe IVH may die and are not at risk of developing BPD (although they will be counted in the BPD/death analysis) and in the sense that hypocapnic infants (due to volutrauma, excessive ventilation; no permissive hypercapnia) may be predisposed to BPD while hypercapnic infants (due to increased CBF; no hypocapnia reducing CBF) may be predisposed to IVH. However, it seems that a higher PCO2 is associated with both severe IVH and BPD (either alone, or in combination with death).

So hypercarbia is not safe, in the sense that it is associated with worse outcome. However, this hypercarbia seems to be the result of increased illness severity rather than due to deliberate "permissive" hypercapnia. If deliberate, one would expect that there would be a negative correlation between Max PCO2 and days of ventilation (babies are extubated sooner), and there would be no correlation between Max PCO2 and Max FiO2 (babies are not sicker). However, we noted the opposite results : a moderate + correlation between Max PCO2 and days of ventilation as well as FiO2 (as well as with illness severity) indicating that a higher CO2 was associated with worse illness.

If one looks at the data, the time-weighted PCO2 is between 48-50, and the SD of PCO2 is around 10. So it seems we are already practicing permissive hypercapnia (PCO2 45-55) for the most part. Is it possible to show that targeting a even higher PCO2 is safe (or not)? I suppose if we re-run the regression analysis adjusting for days of ventilation as well as Max FiO2, we may be better able to adjust for respiratory illness severity.

2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

>> This has not been evaluated so far - we have not yet looked at Max, Min, SD, and TW PCO2 by CPAP/Surfactant group or by SpO2 low/high group. Lisa should be able to do this, and it would probably be necessary to add this to the manuscript. However, treatment group was included in both un-adjusted and adjusted analysis and did not seem to be associated with outcomes of Sev IVH/death or BPD/death (although they may certainly show up when we look at other outcomes). There was no interaction between SpO2 group and Max CO2 in the regression model for these two outcomes.

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

>> I am not sure about the authorship policy - perhaps Dr. Higgins can weigh in on this. In the past year, I remember we did presenting author followed by "for the SUPPORT study group and the NICHD NRN" for the abstract, with all authors listed on the resulting presentation and manuscript.

Thanks,  
Ambal

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]

**Sent:** Sat 10/30/2010 4:59 PM  
**To:** Namasivayam Ambalavanan  
**Cc:** Walsh, Michele; Michael Cotten; Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran; Wrage, Lisa Ann  
**Subject:** RE: PAS ABSTRACT: First draft

I made a few more suggestions with tracking changes. Sometimes it's hard to see what's been done with tracking changes. Feel free to ignore if they don't make sense when "accepted".

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

---

**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Saturday, October 30, 2010 10:18 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Hi Ambal; Attached are my comments in track change. I worked on shortening it.

I have two questions that I think are pertinent:

1. An important clinical question that this data set could answer is what level of Co2 management minimizes the risk of two competing outcomes: bpd and sever IVH? another way: is hypercarbia safe?
2. Did our randomization and management strategy produce differences in CO2 levels during the first 14 days of life? (I realize this may not be the focus of your abstract, but we in the NRN and others are going to want to know.)

Also: need to look at authorship policy- not sure you can have 2 authors from same center as 1-2.

Best Michele

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Fri 10/29/2010 5:28 PM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Walsh, Michele; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT: First draft

Dear All,

Attached is the first full draft of the PAS abstract on PaCO2 in relation to outcome from the SUPPORT trial. The analysis was rather complex, and is still ongoing (Thanks to Lisa!). We are currently at 107% of space available and will have to trim a bit (let me know how). Do let me have your comments. (Wally – can we send it on to the GDB and SUPPORT subcommittees)?

Thanks,  
Ambal

N. Ambalavanan MD

Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

**Mailing Address:**

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619 South 19th Street  
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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

---

**From:** Namasivayam Ambalavanan  
**Sent:** Saturday, October 23, 2010 7:16 AM  
**To:** Namasivayam Ambalavanan; Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Perhaps we can make some adjustment for respiratory illness severity by using mode of ventilation (HFV/CV yes or no; nasal SIMV or CPAP yes or no; using data on NG07-GDB) and time-weighted highest FiO2 (using highest FiO2 on day 1, 3, 7, and 14; using data on NG07). Would we have all this information in the GDB for the years of SUPPORT?  
Ambal

---

**From:** Namasivayam Ambalavanan  
**Sent:** Fri 10/22/2010 8:58 PM  
**To:** Michael Cotten; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon; Seetha Shankaran  
**Subject:** RE: PAS ABSTRACT

Good point. It is always difficult to determine if hypercapnia is deliberate (permissive) or if it is secondary to severe lung disease (high illness severity). Would it be possible to add independent variables to the regression model to deal with this or have some way to adjust for illness severity? Ideally, one would use mean airway pressure and FiO2 (perhaps averaged over the 14 days when the blood gases were measured) for studies of PaO2 and minute ventilation (perhaps peak pressure and ventilator rate) to evaluate PaCO2. However, I don't find that these variables were recorded for SUPPORT or for GDB. So although it is evident that higher PaCO2 were associated with severe IVH, BPD etc, one would not know if this is the result of permissive hypercapnia or because the infants were sicker. Adjustment for BW, gender would take care of some of this as smaller infants and boys are likely to be sicker.  
Ambal

---

**From:** Michael Cotten [<mailto:cotte010@mc.duke.edu>]  
**Sent:** Fri 10/22/2010 7:57 PM  
**To:** Namasivayam Ambalavanan; Wrage, Lisa Ann; ambal  
**Cc:** Abhik Das; Gantz, Marie; Wally Carlo, M.D.; Kennedy, Kathleen A; Abbot Laptook; NIH; Michele Walsh; Matt Laughon

**Subject:** Re: PAS ABSTRACT

Is there a way to have an interaction term between vent support level x co2? Some babies are easily hyperventilatable, and sometimes practitioners allow co2 to be high on min settings,,,and those kids are probably way different than kids on high settings or hfv who remain hypercarbic,,

Mc

---

**From:** "Namasivayam Ambalavanan" [NAmbalavanan@peds.uab.edu]  
**Sent:** 10/22/2010 03:59 PM EST  
**To:** "Wrage, Lisa Ann" <wrage@rti.org>; <ambal@uab.edu>  
**Cc:** "Das, Abhik" <adas@rti.org>; "Gantz, Marie" <mgantz@rti.org>; "Wally Carlo, M.D." <WCarlo@peds.uab.edu>; "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>; "Laptook, Abbot" <ALaptook@WIHRI.org>; "Higgins, Rosemary \ (NIH/NICHD) [E]" <higginsr@mail.nih.gov>; <Michele.Walsh@UHhospitals.org>; Michael Cotten; "Laughon, Matthew M" <matt\_laughon@med.unc.edu>  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,

(cc: all co-authors on the project, as someone will probably have better ideas)

Thank you very much for the unadjusted results. I looked over them and they are highly interesting. As hypothesized, extremes of PaCO<sub>2</sub> (especially higher PaCO<sub>2</sub> and fluctuating PaCO<sub>2</sub>) were associated with severe IVH and BPD (either alone or in combination with death). Unlike previous studies (Kraybill, Garland etc), hypocapnia alone was not associated with BPD or death/BPD.

About what to do now, I think the primary question is whether PaCO<sub>2</sub> is associated with bad outcomes (severe IVH/death or BPD/death) after adjustment for other variables including oxygenation. For the abstract, as we are limited in space (word count for abstract) as well as in time to do all the proposed analyses, the most direct way to answer the primary question may be Aim 2 (c), which is: Multivariable regression analysis will be done for the outcomes of Severe IVH/death and BPD/death using maximal PaCO<sub>2</sub>, minimal PaCO<sub>2</sub>, time-weighted PaCO<sub>2</sub>, and SD of PaCO<sub>2</sub> as independent continuous variables with actual time-weighted PaO<sub>2</sub> (oxygenation) in the first 14 days as another independent variable.

Other variables included in the model will be birth weight, gender, race (NH White vs. others), prenatal steroids, pregnancy induced hypertension, PPRM, 1 and 5 min Apgar scores (if <3), prophylactic indocin, and vaginal delivery, as well as CPAP or surfactant group. (we would not need High or Low saturation group as we are including actual PaO<sub>2</sub> for oxygenation level) (Also, don't know if we need to have prenatal steroids as a variable even though it is a known factor, for >95% of the kids got steroids).

The results of the logistic regression should give us an idea of the association of the PaCO<sub>2</sub> variables with outcome, after adjustment for the other variables. We probably do not need PaCO<sub>2</sub> values adjusted for the other variables, but the Odds Ratios and CI should be enough and perhaps an estimate of how much these variables contribute to the outcome. Interaction terms can tell us the interaction between PaCO<sub>2</sub> and oxygenation. One issue that we may need to address is of correlation/ collinearity between the different PaCO<sub>2</sub> terms (Abhik – any

suggestions?). Also, we had discussed that if the relationship of PaCO<sub>2</sub> to outcome is not strictly linear/logical, we may need a different type of model (polynomial terms/piecewise linear model).

A table showing the rates of the outcomes (BPD/death, BPD in survivors, Severe IVH, Severe IVH in survivors) by CO<sub>2</sub> category (hypocapnia, hypercapnia, fluctuator, normocapnia) may be useful, along with p-values for the comparison across CO<sub>2</sub> categories and the numbers in each CO<sub>2</sub> category. It would also be necessary to show in the text of the abstract the threshold for hypocapnia (e.g. below 38 or 35 mm Hg etc), hypercapnia (e.g. above 55 or 64 mm Hg etc).

Any comments/suggestions from Lisa, Abhik, Wally, other authors will be much appreciated,

Thanks,  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

**Mailing Address:**

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619 South 19th Street  
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Fax Office (205) 934-3100 Lab (205) 996 2333  
Email [ambal@uab.edu](mailto:ambal@uab.edu)

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Friday, October 22, 2010 2:48 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

I have attached the unadjusted results that I promised and along with a brief summary of what was done. Please let me know if you have any questions. Also, while you are reviewing these please think about what adjusted results you would like to present in your abstract. Since there are 5 CO<sub>2</sub> variables of interest and 4 outcomes of interest (=potentially 5x4 models) and time is getting really tight I would appreciate if you could consider a subset of adjusted results or at least prioritize.

Thanks and have a great weekend.

Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Wednesday, October 20, 2010 10:58 AM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.

**Subject:** RE: PAS ABSTRACT

Sure - just to clarify. Capping is ok.  
Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Wed 10/20/2010 9:42 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Ambal,

Thanks for the response. Regarding the time-weighted CO<sub>2</sub>, Wally and Marie did decide to cap the amount of time that on CO<sub>2</sub> level represents (see the emails below). One of the reasons why I originally asked about a cap is that if there are large gaps between blood gases it made me wonder if there was likely a change in the baby's status that inspired an order for a blood gas (?). In that case the result would not necessarily represent the long period between the blood gases. I suppose that we can't know what happened in each case. Anyway, I did want to share the extra information in these emails with you in case it made any difference.

And fyi, I am filling out your tables.  
Thanks.  
Lisa

Marie:

It makes sense. I think we should use 24 hours. I dont know what Ambal asked for his analysis but I think this makes the most sense as on sick infants, generally a blood gas is obtained per day at least.

Wally

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

**From:** Gantz, Marie <[mgantz@rti.org](mailto:mgantz@rti.org)>  
**Sent:** Tuesday, October 19, 2010 7:29 PM  
**To:** Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; Finer, Neil <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>  
**Cc:** Das, Abhik <[adas@rti.org](mailto:adas@rti.org)>; Wrage, Lisa Ann <[wrage@rti.org](mailto:wrage@rti.org)>  
**Subject:** RE: PAS ABSTRACT

Wally,

This question is similar to one Lisa asked Ambal when she was calculating time weighted CO<sub>2</sub> for his paper. When we look at the actual times of CO<sub>2</sub> data collection, there are gaps between measurements of up to 300 hours (12.5 days). Do we want to establish a cut-off so that a single CO<sub>2</sub> measurement cannot account for more than X hours in the time weighted average? Below are percentiles for the number of hours between

**CO2 measurements:**

50th 8.5  
75th 12  
90th 21  
95th 25.5  
99th 80  
100th 300

If we established a cut-off (say, 24 hours) we could still use all of the available CO2 data - if the gap between measurements was greater than our cut-off then we would just weight the measurement after the gap by the maximum number of hours. (So, if the gap was 300 hours and our maximum was 24, then the measurement after the gap would account for 24 hours in our weighted average calculations).

Does that make sense? Is there a cut-off value you think is reasonable, or do you want to allow the CO2 values to be weighted by up to 300 hours in the weighted averages?

Thanks,  
Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 15, 2010 2:56 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,

Thank you for the email.

1) I think it is ok to not cap the amount of time. We can have whatever the actual duration is as 95% of them will be 1 day or less. If we cap it we will have an unknown/missing variable for the rest of the time.

2) I think PROM>24h is ok

3) From a biological sense, I think if we want to collapse race, it would be best to do it as non-hispanic white vs. other, or non-hispanic black vs. other.

4) As these are ELBW infants, I think Apgar 1 min <3 (0-2) would be a good threshold.

Ambal

**From:** Wrage, Lisa Ann [mailto:wrage@rti.org]  
**Sent:** Friday, October 15, 2010 1:46 PM  
**To:** Namasivayam Ambalavanan; ambal@uab.edu  
**Cc:** Das, Abhik; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** FW: PAS ABSTRACT

Hi Ambal.

I am nearly finished getting your analysis data together and I have a few questions about specific variable definitions:

For time-weighted CO2 I am using actual blood gas time, where available. If actual time is not available I am using protocol time (i.e. 8:00, 16:00, or 23:59). The median time between blood gases is 8 hours, the mean is 12.4, the 95<sup>th</sup> %ile is 25.1 hours and the 99<sup>th</sup> %ile is 79.8 hours, so there are some infants who have gaps between blood gasses that are > 1 day, is this ok or would you like to cap the amount of time that one CO2 level represents?

How do you want to define premature rupture of membranes? We commonly use ROM > 24 hours prior to birth, would this be ok or would you prefer something else?

How would you like to define race? Right now I have non-hispanic black, non-hispanic white, Hispanic, other. We also may want to collapse categories for the models.

Would you like to categorize apgar scores (e.g. 1 min apgar <3, or <5)?

That is all the questions that I have for now.

I expect to send you some unadjusted results next week and then start working on adjusted results.

Thanks,  
Lisa

---

**From:** Wrage, Lisa Ann  
**Sent:** Tuesday, October 05, 2010 2:45 PM  
**To:** 'Namasivayam Ambalavanan'; ambal@uab.edu  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,

Okay, thank you, these clarifications have been very helpful.

Now my tentative plan is to:

- 1) create the CO2 variables of interest and get the rest of the necessary analysis data together
- 2) provide unadjusted result similar to those in your 2007 Pediatrics paper, Table 2, for each CO2 variable / outcome combination
- 3) then move on to the models for adjusted results.

Let me know if this sounds ok. It will take me a while to complete #1, so don't be concerned if you don't hear from me for a little while. I will of course be in touch if any questions come up.  
Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 2:38 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
My answers (>>) are below your questions (\*\*)

Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 12:36 PM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Ambal,  
Thank you, this is helpful, I have a few more questions (see \*\* below).  
Lisa

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Tuesday, October 05, 2010 12:42 PM  
**To:** Wrage, Lisa Ann; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Lisa,  
(Abhik/Wally/Marie – your comments are also welcome)  
If we are going to do a condensed version for the PAS abstract, these would probably be the priorities:

- 1) Outcomes: Severe IVH, Severe IVH/death, BPD, BPD/death

*\*\*Which BPD definition would you like to use?: Oxygen at 36 weeks, or the physiologic definition.*

>> I think the physiologic definition of BPD would be better, rather than the standard definition, as it is less likely to be affected by center practices

- 2) For Aim (1): determine the association of PaCO<sub>2</sub> in the first 2 weeks with outcomes, we will use PaCO<sub>2</sub> as a continuous variable, with adjustment for other patient characteristics (birth weight, gender, race, pregnancy induced hypertension, premature prolonged rupture of membranes,

antenatal steroids, 1 and 5 minute Apgar scores, indocin in first 24 h, mode of delivery – vaginal vs others, and center) by multivariable regression.

*\*\*Could you please clarify how you like to summarize PaCO<sub>2</sub> over the first two weeks as a continuous variable here? Did you want to use all 5 continuous measures that you used in a previous publication (max, min, time-weighted, Standard deviation, difference)? Or could we use a subset of these?*

**>> I think max, min, time-weighted, and standard deviation should be ok.**

- 3) For Aims (2) and (3), to determine the association of high/low PaCO<sub>2</sub> with outcomes, we will divide infants into quartiles based on their maximum PCO<sub>2</sub> and their minimum PCO<sub>2</sub> over the first two weeks. The infants in the highest quartile of max PCO<sub>2</sub> are "hypercapnic", and we can probably identify the threshold that divides them from the lower three quartiles. The infants in the lowest quartile of minimum PCO<sub>2</sub> will be the "hypocapnic" ones, and we can also identify a threshold for them. There will be some "fluctuators" who are in both groups. "Normocapnia" infants are those who in the middle two quartiles of Max PCO<sub>2</sub> and minimum PCO<sub>2</sub>. The outcomes will be assessed in the low and high SpO<sub>2</sub> groups in relation to PaCO<sub>2</sub> status (hypercapnia, hypocapnia, or fluctuators, vs. the normocapnia infants).

*\*\*So, just to summarize, here we are using a 4-level categorical variable with categories of: Hypercapnic (in upper quartile of max PCO<sub>2</sub>), >> Yes. fluctuators will be a subset of this group, so we should probably exclude fluctuators [Hypercapnia only, not fluctuators]. Hypocapnic (in lower quartile of min PCO<sub>2</sub>), >> Yes. As above, I think we should have hypocapnia only, not fluctuators.*

*Fluctuators (in both upper quartile of max PCCO<sub>2</sub> lower quartile of min PCO<sub>2</sub>)>> Yes.  
Normocapnic (in middle two quartiles of max PCO<sub>2</sub> AND min PCCO<sub>2</sub>)*

*To define Max PCO<sub>2</sub> and Min PCO<sub>2</sub> do you simply want me to use the maximum and minimum value of all values of PCO<sub>2</sub> for each infant using PCO<sub>2</sub> recorded during the 1<sup>st</sup> two weeks on the SUPP05 form?*

**>> Yes**

- 4) For Aims (2) and (3), we are also planning (if time permits), multivariable analysis using maxPCO<sub>2</sub>, minPCO<sub>2</sub>, time-weighted PCO<sub>2</sub>, and SD of PCO<sub>2</sub> as independent continuous variables with SUPPORT group assignment

**\*\*OK.**

**>>Great!**

Thanks,  
Ambal

---

**From:** Wrage, Lisa Ann [<mailto:wrage@rti.org>]  
**Sent:** Tuesday, October 05, 2010 10:32 AM  
**To:** Namasivayam Ambalavanan; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Subject:** RE: PAS ABSTRACT

Hi Dr. Ambalavanan,

I have had a chance to look over your protocol and since there is a lot going on in it I think that the first thing that we need to do is to prioritize analyses for the abstract (basically pare it down to work that is crucial for the abstract, and that can be done in a couple of weeks) and then clarify some definitions.

Specifically, it looks like your hypotheses focus on the association of high / low CO2 to outcomes, plus how high / low CO2 interacts with SpO2. I see quite a few CO2 related variables discussed, but I don't see anything that clearly defines high / low CO2 (although I do see some potential ranges discussed, such as <30 or >60 torr). Do we need all of these CO2 related variables for the abstract? The CO2 data may be fairly complex to work with, is there a relatively straightforward way we could define high / low CO2 groups to start?

Also, it looks like you are focusing on 9 outcomes: Severe IVH, ROP, BPD, NEC, death, plus death/Severe IVH, death/ROP, death/ BPD, death/NEC. Could we focus on a subset of these outcomes for the abstract?

You also mention other variables of interest, but the list is incomplete: "birth weight, gestational age, sex, antenatal steroids, etc. ", could you please provide a complete list?

Thank-you,  
Lisa

Lisa Wrage, MPH  
Research Statistician  
Statistics & Epidemiology  
RTI International  
[wrage@rti.org](mailto:wrage@rti.org)  
919-220-2653

---

**From:** Namasivayam Ambalavanan [<mailto:NAmbalavanan@peds.uab.edu>]  
**Sent:** Friday, October 01, 2010 11:14 AM  
**To:** Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Hi Lisa, Marie,  
What do we need to start the project? Do you need any further information (other than the protocol you have)? Should we have a conference call sometime?  
Ambal

N. Ambalavanan MD  
Division of Neonatology,  
Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology

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**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Tuesday, September 21, 2010 3:55 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** Wally Carlo, M.D.; Wrage, Lisa Ann; Gantz, Marie  
**Subject:** RE: PAS ABSTRACT

Ambal:

Lisa Wrage will work on this analysis. She will coordinate with Marie as well.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, September 21, 2010 11:15 AM  
**To:** Ambal ([ambal@uab.edu](mailto:ambal@uab.edu))  
**Cc:** Wally Carlo, M.D.; Das, Abhik  
**Subject:** PAS ABSTRACT

Ambal -

Your PAS abstract has been approved for analysis. Your abstract is a second level of priority for RTI given the number of SUPPORT abstracts.

Please contact Abhik Das by SEPTEMBER 24 for statistician assignment.

**For abstracts that are approved for data analysis, but continue to need final approval from one or more subcommittees, please arrange to have this information to the appropriate subcommittees by October 19, 2010 in order to allow ample time for potential additional analysis.**

November 8, 2010– Final abstracts to NICHD for clearance  
Mid-November– PAS deadline  
April 30- May 3, 2011 -PAS meeting – Denver, Colorado

Certainly proposals and protocols are encouraged prior to these dates.

Let me know if there are any questions

Thanks

Rose

Rosemary D. Higgins, MD  
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**Title:**

**Association of PaCO<sub>2</sub> with outcomes in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)**

**Authors:**

Namasivayam Ambalavanan MD<sup>1</sup>; Waldemar A. Carlo MD<sup>1</sup>; Lisa A. Wrage MPH<sup>2</sup>; Abhik Das PhD<sup>3</sup>; Matthew Laughon MD MPH<sup>4</sup>; C. Michael Cotten MD MHS<sup>5</sup>; Kathleen A. Kennedy MD MPH<sup>6</sup>; Abbot R. Laptook MD<sup>7</sup>; Seetha Shankaran MD<sup>8</sup>; Michele C. Walsh MD MS<sup>9</sup>; Rosemary D. Higgins MD<sup>10</sup>; For the SUPPORT Study Group of the NICHD Neonatal Research Network

**Author Affiliations:**

<sup>1</sup>Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; <sup>2</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; <sup>3</sup>Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD; <sup>4</sup>Department of Pediatrics, University of North Carolina, Chapel Hill, NC; <sup>5</sup>Department of Pediatrics, Duke University, Durham, NC; <sup>6</sup>Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; <sup>7</sup>Department of Pediatrics, Women and Infants Hospital, Providence, RI; <sup>8</sup>Department of Pediatrics, Wayne State University, Detroit, MI; <sup>9</sup>Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; <sup>10</sup>*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

**Short Title: PaCO<sub>2</sub> and IVH**

**Abbreviations:** BSID: Bayley Scales of Infant Development; CP: Cerebral palsy; IVH: Intraventricular hemorrhage; sIVH: severe intraventricular hemorrhage; NICU: neonatal intensive care unit; NDI: Neurodevelopmental impairment; PIH: Pregnancy Induced Hypertension; PVL: Periventricular leukomalacia

**Keywords:** Infant, premature; Infant mortality; Infant, Premature, Diseases/epidemiology; Predictive value of tests; Prognosis; Intracranial hemorrhage; Blood Gas Analysis

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**Funding source:** Supported by grants from the National Institute of Child Health and Human Development and the Department of Health and Human Services with co-funding from the National Heart, Lung, and Blood Institute (NHLBI) (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27871, U10 HD27880, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, U10 HD53124) and from the National Institutes of Health (M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, M01 RR125, M01 RR633,

M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 TR93, UL1 TR142, UL1 TR442, UL1 TR454).

**Conflicts of interest:** The authors have no financial relationships or conflicts of interest relevant to this article to disclose.

**Word count:** abstract: 249; text of manuscript: 3106 (Introduction, Methods, Results, and Discussion).

**What's known on this subject:** Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) might contribute to or be associated with several clinical outcomes of prematurity such as intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, and subsequent neurodevelopmental impairment.

**What this study adds:** Higher  $\text{PaCO}_2$  and greater fluctuation in  $\text{PaCO}_2$  were associated with severe intraventricular hemorrhage, bronchopulmonary dysplasia, and neurodevelopmental impairment or death. The correlation of  $\text{PaCO}_2$  with  $\text{FiO}_2$  and days of ventilation support higher maximum  $\text{PaCO}_2$  as a marker of illness severity in premature infants

**Ambal---Pages need to be numbered?**

**ABSTRACT:**

**Objective:** To determine the association of PaCO<sub>2</sub> with severe intraventricular hemorrhage (sIVH), bronchopulmonary dysplasia (BPD), and neurodevelopmental impairment (NDI) at 18-22 months in extremely premature infants. **Methods:** Blood gases from postnatal days 0-14 were analyzed in 1316 infants 24 0/7 to 27 6/7 wks GA randomized in the SUPPORT trial to different oxygenation (SpO<sub>2</sub> targets of 85-89% vs 91-95%) and ventilation strategies. Five PaCO<sub>2</sub> variables were defined: minimum [Min], maximum [Max], standard deviation, time-weighted, and a 4 level categorical variable (hypercapnic [highest quartile of Max PaCO<sub>2</sub>], hypocapnic [lowest quartile of Min PaCO<sub>2</sub>], fluctuators [both hypercapnia and hypocapnia], and normocapnic [middle two quartiles of Max and Min PaCO<sub>2</sub>]). Adjusted and unadjusted analyses compared PaCO<sub>2</sub> variables for infants with and without sIVH, BPD, and NDI (+/- death).

**Results:** sIVH, BPD, and NDI (+/- death), as well as death were more common in hypercapnic infants and fluctuators. The relationship of Max PaCO<sub>2</sub> with outcomes persisted after adjustment (For increase of 10 mmHg: sIVH/death: OR 1.39 [1.27-1.53]; BPD/death: OR 1.57 [1.41-1.75]; NDI/death: OR 1.38 [1.25-1.52], Death: OR 1.36 [1.22-1.51], all p <0.0001). A higher time-weighted PaCO<sub>2</sub> was associated with sIVH/death only if the SpO<sub>2</sub> was lower, and fluctuators were at higher risk for BPD/death only in the higher SpO<sub>2</sub> target group. Max PaCO<sub>2</sub> was positively correlated with maximum FiO<sub>2</sub> (r<sub>s</sub>0.55, p<0.0001) & ventilator days (r<sub>s</sub>0.61, p<0.0001). **Conclusions:** Higher PaCO<sub>2</sub> was associated with sIVH, BPD, and NDI (+/- death). Correlation of PaCO<sub>2</sub> with FiO<sub>2</sub> and ventilator days supports higher Max PaCO<sub>2</sub> as a marker of illness severity.

**(Abstract Word Count = 249)**

## MANUSCRIPT TEXT

### INTRODUCTION

Variations in arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are associated with and may possibly contribute to several important clinical outcomes of prematurity such as intraventricular hemorrhage (IVH)<sup>1</sup>, periventricular leukomalacia (PVL)<sup>2,3</sup>, bronchopulmonary dysplasia (BPD)<sup>4</sup>, and subsequent neurodevelopmental impairment (NDI)<sup>5</sup>. Increased  $\text{PaCO}_2$  increases cerebral blood flow,<sup>6-8</sup> while decreased  $\text{PaCO}_2$  reduces cerebral blood flow, increases cerebral fractional oxygen extraction, and decreases cerebral electrical activity.<sup>9</sup> We have previously shown that both high and low  $\text{PaCO}_2$  levels and wide fluctuations in  $\text{PaCO}_2$  are associated with a higher risk of severe IVH (sIVH; IVH Grades III or IV).<sup>1</sup> Periventricular leukomalacia (PVL) is strongly associated with hypocapnia.<sup>2,3,10</sup>

Cerebral blood flow decreases slightly with increased oxygenation<sup>8</sup> but the interactions between  $\text{PaCO}_2$  and oxygenation have not been assessed in preterm infants. Lung injury might be reduced by tolerance of a higher  $\text{PaCO}_2$ <sup>4,11,12</sup> as well as a lower oxygen saturation target,<sup>13</sup> permitting earlier weaning from mechanical ventilation and reduced volutrauma. The combination of a higher  $\text{PaCO}_2$  (permissive hypercapnia) as well as a lower  $\text{PaO}_2$  (targeting a lower  $\text{SpO}_2$  range) might be associated with a reduction in BPD, more than with either permissive hypercapnia or a lower oxygen saturation target alone.

The NICHD Neonatal Research Network SUPPORT trial enrolled infants 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation and compared outcomes in infants randomly assigned to oxygen saturation targets of either 85-89% or 91-95%, while also randomly allocated to either early CPAP and a limited ventilation strategy (a  $\text{PaCO}_2 > 65$  mm Hg permitted intubation, while a  $\text{PaCO}_2 < 65$  mm Hg with a  $\text{pH} > 7.20$  was a mandatory extubation criterion) or intubation and surfactant within 1

hour after birth (a  $\text{PaCO}_2 < 50$  mm Hg with a  $\text{pH} > 7.30$  was a mandatory extubation criterion).<sup>13, 14</sup> Death and other major outcomes did not differ significantly by CPAP vs. intubation/surfactant groups although infants in the CPAP (higher  $\text{PaCO}_2$  target) group less frequently required surfactant, intubation, and postnatal steroids, required fewer days of mechanical ventilation, and were more likely to be alive and free of mechanical ventilation by day 7 after birth. Between the oxygenation target groups, death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60;  $p = 0.04$ ) while severe retinopathy among survivors occurred less often in these infants (8.6 vs. 17.9%; RR 0.52; CI 0.37, 0.73;  $p < 0.001$ ), without significant differences in other outcomes although a trend for a reduction in BPD (physiological definition)<sup>15, 16</sup> by 36 wk was noted in the lower saturation target group (38% vs. 41.7%; RR 0.92; CI 0.81, 1.05).<sup>13</sup> There were no significant differences in the composite outcome of death or neurodevelopmental impairment (NDI) among infants in any of the treatment groups.<sup>17</sup>

It is possible that clinical outcomes that are not significantly different by  $\text{SpO}_2$  target groups might be different when the combination of  $\text{PaCO}_2$  and  $\text{SpO}_2$  is analyzed. We hypothesized that both extremes of  $\text{PaCO}_2$  would be associated with severe IVH, and that effect modification of  $\text{SpO}_2$  will be observed, with hypercapnia associated with sIVH in the low but not high  $\text{SpO}_2$  group. We also hypothesized that BPD would be lower in infants with hypercapnia and low  $\text{SpO}_2$ , and that higher  $\text{PaCO}_2$  will be associated with a higher risk of NDI.

## **PATIENTS AND METHODS**

### **Patient characteristics:**

This was a secondary analysis of data from infants (N=1316) enrolled in the SUPPORT trial.<sup>13, 14</sup> Neonatal information collected for the SUPPORT trial included birth weight, gender, race/ethnicity, maternal information, respiratory support, blood gas measurements, clinical outcomes, and treatment. The baseline characteristics of this population<sup>13</sup> and characteristics of the follow-up cohort<sup>17</sup> have been previously reported.

### **PaCO<sub>2</sub> variables**

Five PaCO<sub>2</sub> variables were defined for this observational study, using routine clinical blood gas measurements that were not governed by study protocol. Data were collected on all PaCO<sub>2</sub> from blood gases done at 3 daily time points (~~maximum~~) closest to 8 am, 4pm, and midnight on postnatal days 1-14: minimum level, maximum level (Max PaCO<sub>2</sub>), standard deviation, time-weighted, and a 4 level categorical variable. Time-weighted PaCO<sub>2</sub> was calculated as described previously.<sup>1</sup> Ambal, can you briefly describe it? That would help both reviewer and the readers? Time between blood gases was capped at 24 hours (~5% of all time difference measurements) so any one blood gas represents no more than 24 hours of time. The median (mean; 5<sup>th</sup>-95<sup>th</sup> centiles) of number of blood gases on study day 1 per infant was 2 (2, 1-3), 3 (2.4, 1-3) on study day 3, 2 (2.1, 1-3) on study day 7, and 2 (2, 1-3) on study day 14. Infants were also categorized into 4 groups: hypercapnic, hypocapnic, fluctuators, and normocapnic. This was accomplished by first separately ranking the maximum and minimum PaCO<sub>2</sub> levels over days 1-14 into quartiles. Infants with minimum PaCO<sub>2</sub> levels in the lowest quartile who were not also in the highest quartile of maximum PaCO<sub>2</sub> level were then categorized as 'hypocapnic'. Infants with maximum PaCO<sub>2</sub> levels in the highest quartile who were not also in the lowest quartile of minimum PaCO<sub>2</sub> level were categorized as 'hypercapnic'. Infants in both the lowest quartile of minimum PaCO<sub>2</sub> and the highest quartile of maximum PaCO<sub>2</sub> were

categorized as 'fluctuators', and the remaining infants, those whose minimum PaCO<sub>2</sub> level fall in quartiles 2-4 and maximum PaCO<sub>2</sub> levels fall in quartiles 1-3 were categorized as 'normocapnic'.

### **Other variables**

Maternal hypertension was defined as pregnancy induced hypertension. Premature rupture of membranes was defined as rupture of membranes greater than 24 hours prior to birth. Prenatal steroids were defined as any use of antenatal steroids. Maximum FiO<sub>2</sub> was defined as the maximum of FiO<sub>2</sub> at 24 hours, day 3, 7, 14 and severe illness was defined *a priori* as FiO<sub>2</sub> >0.4 and mechanical ventilation for 8+ hours in the 1<sup>st</sup> 14 days. Severe IVH was defined as IVH grade 3-4 (the most severe grade identified in the first 28 days),<sup>18</sup> and BPD was defined using the physiologic definition at 36 w PMA.<sup>15, 16</sup> Neurodevelopmental impairment was defined as any of the following: a cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) of less than 70, a modified Gross Motor Function Classification System (GMFCS) score of 2 or higher, moderate or severe cerebral palsy, hearing impairment, or bilateral visual impairment.<sup>17</sup>

### **Statistical Analysis**

The PaCO<sub>2</sub> and other variables were compared by each of 7 outcomes: severe IVH, severe IVH or death, BPD, BPD or death, NDI, and NDI or death, and death by discharge. Specifically, the PaCO<sub>2</sub> and other variables for infants with the specified outcome were compared to those who did not have the outcome. Statistical significance (p<.05) was assessed by Chi Square tests for categorical variables and the Wilcoxon two sample test for continuous variables. In keeping with the hypothesis generating goals of this observational study, no adjustments were made for multiple comparisons.

Adjusted results for the Max PaCO<sub>2</sub>, the 4 level PaCO<sub>2</sub> categorical variable, as well as time-weighted PaCO<sub>2</sub> were obtained using generalized estimating equation (GEE) models for the binary outcomes with robust standard error estimation which takes into account correlations within multiple-birth clusters, thus accounting for the fact that multiple births were randomized to the same treatment arm in the SUPPORT trial. Variables included in the models along with the PaCO<sub>2</sub> variable were: birth weight, GA group, gender, race, prenatal steroid use, pregnancy induced hypertension, rupture of membranes >24 hours, and center. SUPPORT trial treatment group variables (High/Low SpO<sub>2</sub>; CPAP/ventilator) variables were also included in the model that contained Max PaCO<sub>2</sub> and the model that contained the 4 level PaCO<sub>2</sub> variable. Interactions of these PaCO<sub>2</sub> and treatment group variables were also included to assess if the effect of PaCO<sub>2</sub> varied by treatment group. A variable for actual median SpO<sub>2</sub> in the first 14 days was included in the model that contained time-weighted PaCO<sub>2</sub>. The interaction of these two variables was included to assess if the effect of time-weighted PaCO<sub>2</sub> varied by level of actual median oxygen saturation. Results are expressed as adjusted odds ratios and 95% confidence intervals.

## RESULTS

### Adjusted analysis for Severe IVH/Death (Table 1):

Max PaCO<sub>2</sub> was significantly associated with higher odds of sIVH/death (OR 1.39, 95% CI 1.27-1.53 for an increase in Max PaCO<sub>2</sub> of 10 mmHg,  $p < 0.0001$ ). No interaction was found between PaCO<sub>2</sub> category (Hypocapnic, Hypercapnic, Fluctuator, or Normocapnic) and treatment group (High or Low SpO<sub>2</sub>), but the interaction term for time-weighted PaCO<sub>2</sub> and median SpO<sub>2</sub> in the first 14 days was significant ( $p < 0.05$ ), with a higher OR associated with a lower median SpO<sub>2</sub> (OR of 1.6 for median SpO<sub>2</sub> of 91, 1.44 for SpO<sub>2</sub> of 92, 1.30 for SpO<sub>2</sub> of 93, 1.18 for SpO<sub>2</sub>

of 94) indicating that a higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the SpO<sub>2</sub> was lower. Hypercapnic infants and fluctuators had a higher OR for sIVH/death, as compared to normocapnic infants (the reference group) or hypocapnic infants.

Other variables significantly associated (p<0.05) with sIVH/death included: lower birth weight and gestational age, male gender, pregnancy induced hypertension, and center.

Adjusted analysis for BPD/Death (Table 2): I see PIH was associated with lower risk of ICH/death, so should that be restated?

Max PaCO<sub>2</sub> (OR 1.57, 95% CI 1.41-1.75 for an increase in Max PaCO<sub>2</sub> of 10 mmHg, p < 0.0001) and time-weighted PaCO<sub>2</sub> (OR 2.41, 95% CI 1.89-3.09 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg, p < 0.0001) were significantly associated with higher odds of BPD/death. The interaction term between PaCO<sub>2</sub> category and treatment group (High or Low SpO<sub>2</sub>) was significant for fluctuators (p=0.006), with the OR for fluctuators in the High SpO<sub>2</sub> group being 7.4, as compared to 1.18 for the low SpO<sub>2</sub> group.

Other variables significantly associated (p<0.05) with BPD/death included: lower birth weight, male gender, and center.

Adjusted analysis for NDI/Death (Table 3):

Max PaCO<sub>2</sub> (OR 1.38, 95% CI 1.25-1.52 for an increase in Max PaCO<sub>2</sub> of 10 mmHg, p<.0001) and time-weighted PaCO<sub>2</sub> (OR 1.44, 95% CI 1.09-1.90 for an increase in time-weighted PaCO<sub>2</sub> of 10 mmHg, p < 0.0001) were significantly associated with higher odds of NDI/death. No significant interactions were noted between PaCO<sub>2</sub> category and treatment group. Hypercapnic infants and fluctuators had a higher OR for NDI/death, as compared to normocapnic infants (the reference group) or hypocapnic infants. Other variables significantly

associated ( $p < 0.05$ ) with NDI/death included: lower birth weight and gestational age, male gender, PIH, and center.

**Adjusted analysis for Death before discharge (Table 4):**

Max PaCO<sub>2</sub> (OR 1.36, 95% CI 1.22-1.51 for an increase in Max PaCO<sub>2</sub> of 10 mmHg,  $p < .0001$ ) was significantly associated with higher odds of death before discharge. Hypercapnic infants and fluctuators had a higher OR for death, as compared to normocapnic infants (the reference group) or hypocapnic infants. Other variables significantly associated ( $p < 0.05$ ) with death before discharge included: lower birth weight, male gender, PIH, and center.

As higher Max PaCO<sub>2</sub> may be either deliberate (clinician intent for permissive hypercapnia, which may be accompanied by fewer days of mechanical ventilation for comparable illness severity) or due to more severe pulmonary disease (which may be associated with higher max FiO<sub>2</sub>, days of mechanical ventilation, and severe illness), correlations of Max PaCO<sub>2</sub> with max FiO<sub>2</sub>, days of ventilation, and severe illness (as previously defined) were calculated. Max PaCO<sub>2</sub> was positively correlated with both max FiO<sub>2</sub> (Spearman correlation coefficient = 0.55,  $p < 0.0001$ ) and days of ventilation (Spearman correlation coefficient = 0.61,  $p < 0.0001$ ). There was also a significant difference in PaCO<sub>2</sub> level by infants defined as having severe illness (median max PaCO<sub>2</sub>=78) vs. infants defined as having no severe illness (median max PaCO<sub>2</sub>=61),  $p < 0.0001$  by Wilcoxon two sample test.

**Unadjusted Results (Supplemental Tables 1-4):**

All PaCO<sub>2</sub> variables (minimum, maximum, standard deviation, time-weighted, and categorical) were different in the infants with sIVH as compared to those without sIVH. In general, infants who developed sIVH had a lower minimum, higher maximum and greater variation in PaCO<sub>2</sub> as compared to those without sIVH. Max PaCO<sub>2</sub> demonstrated the largest

magnitude of separation, with a difference of almost 10 mm Hg in the mean and median Max PaCO<sub>2</sub> between infants with sIVH and those without sIVH. The magnitude of separation in minimum, standard deviation, and time-weighted PaCO<sub>2</sub> were statistically highly significant ( $p < 0.0001$ ) but clinically small (~2 mm Hg). Bivariate analysis showed that infants who died or developed sIVH had higher maximum, standard deviation, and time-weighted PaCO<sub>2</sub> compared to survivors without sIVH. Results for BPD, BPD or death, NDI, and NDI or death were similar to those for severe IVH and severe IVH or death.

## DISCUSSION

We found that extremes of PaCO<sub>2</sub> were associated with worse outcome (sIVH, BPD, and NDI) in extremely preterm infants. A higher maximum PaCO<sub>2</sub> in the first two postnatal weeks was an independent predictor of worse outcome and was correlated with other indicators of illness severity (maximum FiO<sub>2</sub>, days of ventilation, and severe illness). A higher average PaCO<sub>2</sub> was associated with severe IVH/death only if the SpO<sub>2</sub> was lower. Greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the high SpO<sub>2</sub> and not in the low SpO<sub>2</sub> group.

Our study has the limitation that infants in the SUPPORT trial<sup>13, 14</sup> were not primarily randomized to different specific PaCO<sub>2</sub> ranges as in the randomized trials of permissive hypercapnia<sup>4, 12, 19</sup> but to interventions (Early CPAP vs. intubation/surfactant) with different PaCO<sub>2</sub> goals. Data on corresponding ventilator settings, mean airway pressure, oxygenation index, and ventilation index are not available to determine if reduction of PaCO<sub>2</sub> using higher ventilator settings was associated with better outcome in the SUPPORT trial. This study has the strengths of careful prospective data collection from a large multi-center trial in recent years. Additionally, criteria for intubation and extubation were used in the trial, and trained research

coordinators collected data on blood gases and ventilator settings in addition to other routine clinical variables. Eighteen to 22 month~~Longer-term~~ follow-up was achieved in the majority of infants, and was done by certified trained personnel. No interaction was observed between maximum PaCO<sub>2</sub> and SpO<sub>2</sub> groups, probably because randomization in this trial most likely led to a similar range of PaCO<sub>2</sub> in both SpO<sub>2</sub> groups. It is possible that in the other arm of the factorial trial (CPAP vs. intubation/surfactant), alterations in PaCO<sub>2</sub> secondary to ventilatory interventions might mediate some of the clinical effects observed in SUPPORT.<sup>14</sup>

Previously, we have shown in a single-center retrospective analysis that both high and low PaCO<sub>2</sub> levels and wide fluctuations in PaCO<sub>2</sub> are associated with an increased risk of sIVH.<sup>1</sup> The current study confirms and strengthens these findings in a more recent cohort of infants from multiple centers. While the differences in minimum, time-weighted, and standard deviation of PaCO<sub>2</sub> were statistically significant, they were of small magnitude. Clinically relevant differences (~10 mm Hg) were only noted in the maximum PaCO<sub>2</sub>. As maximum PaCO<sub>2</sub> was correlated with a longer duration of mechanical ventilation and a higher magnitude of oxygen supplementation, it is likely that these infants with higher maximum PaCO<sub>2</sub> had more severe lung disease, rather than due to more aggressive weaning from mechanical ventilation. This is consistent with a higher average PaCO<sub>2</sub> in combination with a lower SpO<sub>2</sub> being associated with severe IVH/death, suggesting that these infants were sicker with greater gas exchange difficulty.

In this cohort, the average (time-weighted) PaCO<sub>2</sub> even in infants without severe IVH was  $\geq 48$  mm Hg with a relatively narrow interquartile range (~10 mm Hg). It is important to note that this closely corresponds to the “permissive hypercapnia” range (45-55 mm Hg) of the initial randomized trial of permissive hypercapnia in preterm infants.<sup>12</sup> Our data indicate clinical practices in academic centers have evolved to maintain PaCO<sub>2</sub> in the permissive hypercapnia

range. However, as the maximum PaCO<sub>2</sub> exceeded this range even in infants without severe IVH, it is apparent that tight control of PaCO<sub>2</sub> within this narrow range is difficult.

A higher maximum and time-weighted PaCO<sub>2</sub> and a greater magnitude of fluctuation in PaCO<sub>2</sub> were associated with a greater risk of BPD and BPD/death. Similar to severe IVH, this is likely due to greater illness severity and more severe lung disease being associated with a higher PaCO<sub>2</sub> rather than because of rapid weaning and physician intent. Although we have shown that hypercapnia is associated with increased illness severity and worse outcomes, hypercapnia within a limited range may not only be acceptable but may in fact be of benefit. Hypercapnia increases CO<sub>2</sub> elimination for a given minute ventilation, due to a higher CO<sub>2</sub> in alveolar air (P<sub>A</sub>CO<sub>2</sub>). Also, due to the Bohr effect, hemoglobin affinity for oxygen decreases with increasing PaCO<sub>2</sub>, and peripheral unloading of oxygen improves with hypercapnia. Hypercapnia also stimulates respiratory drive, which may help in weaning preterm infants from the ventilator. There is also evidence that hypercapnic acidosis may attenuate ventilator-induced lung injury and inflammation by multiple molecular mechanisms.<sup>9, 11, 14</sup> do you think cite 14 should be listed—molecular mechanism were not assessed? However, while recent randomized trials of permissive hypercapnia in preterm infants have demonstrated the safety of mild permissive hypercapnia, no statistically significant reductions in BPD/death have been demonstrated.<sup>4, 11, 12, 19</sup> In the largest randomized trial of permissive hypercapnia to date, which was terminated early due to unanticipated non-respiratory adverse events secondary to dexamethasone therapy, the relative risk for death or BPD in the minimal ventilation versus routine ventilation groups was 0.93 (63% vs. 68%; 95% CI 0.77-1.12, p = 0.43), despite ventilator support at 36 weeks being 1% in the minimal versus 16% in the routine group (p<0.01).<sup>4</sup> An interesting finding in the present study was that greater fluctuation in PaCO<sub>2</sub> was associated with BPD/death only in the

high SpO<sub>2</sub> but not in the low SpO<sub>2</sub> group. It is speculated that higher oxygen exposure in the high SpO<sub>2</sub> group may interact with volutrauma/atelectrauma associated with fluctuating PaCO<sub>2</sub> possibly increasing the risk for BPD/death.

Max PaCO<sub>2</sub> was also significantly associated with higher NDI/death, confirming our previous single-center study.<sup>5</sup> This association may be secondary to Max PaCO<sub>2</sub> being an indicator of illness severity, perhaps serving as a surrogate marker for various injurious stimuli such as circulating cytokines.<sup>20</sup> Alterations in PaCO<sub>2</sub> may also mediate brain injury directly. A sudden marked increase in cerebral blood flow secondary to a spike in PaCO<sub>2</sub><sup>6-8</sup> may result in sIVH<sup>1</sup> and contribute to NDI. A reduction in cerebral blood flow due to decreased PaCO<sub>2</sub><sup>9</sup> may contribute to lower white matter perfusion and result in periventricular leukomalacia (PVL).<sup>2, 3, 10</sup> The brain injury associated with extremes of PaCO<sub>2</sub> may not always be evident on cranial ultrasound, as subtle white matter damage may occur without obvious IVH or PVL.<sup>21, 22</sup>

In conclusion, our work demonstrates that Max PaCO<sub>2</sub> is a marker of illness severity and is an independent predictor of worse outcome in extremely preterm infants. Therefore, in a manner similar to oxygenation index or PaO<sub>2</sub>, Max PaCO<sub>2</sub> may be useful for risk-stratification in clinical trials or for prognosis. It is important to remember that while these results are valid for the first two weeks of age in ELBW infants, the association of PaCO<sub>2</sub> with outcomes at later time points and in other populations needs to be determined.

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**Table 1: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of severe IVH/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.39 (1.27-1.53)	<.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.11 (0.73-1.67)	0.63
<b>Hypercapnic</b>	2.60 (1.77-3.82)	<.0001
<b>Fluctuator</b>	2.81 (1.68-4.72)	<.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub>**</b> <b>(per 10 mm Hg)</b>		
<b>Median SpO<sub>2</sub>=91</b>	1.60 (1.17-2.17)	.0028
<b>Median SpO<sub>2</sub>=94</b>	1.18 (0.85-1.62)	0.32

\*\* interaction term for time-weighted PaCO<sub>2</sub> x Median SpO<sub>2</sub> in the first 14 days was significant (p=0.048) indicating that the effect of time-weighted PaCO<sub>2</sub> depended on level of Median SpO<sub>2</sub>.

**Table 2: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of BPD/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.57 (1.41-1.75)	<.0001
<b>PaCO<sub>2</sub> Category: <u>High SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	0.73 (0.46-1.16)	0.18
<b>Hypercapnic</b>	2.54 (1.41-4.60)	0.0019
<b>Fluctuator</b>	7.4 (2.6-21.0)	0.0002
<b>Normocapnic</b>	REFERENCE	-
<b><u>Low SpO<sub>2</sub></u></b>		
<b>Hypocapnic</b>	1.01 (0.63-1.63)	0.96
<b>Hypercapnic</b>	3.38 (1.93-5.93)	<.0001
<b>Fluctuator</b>	1.18 (0.51-2.70)	0.70
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	2.41 (1.89-3.09)	<.0001

\*\* interaction term for PaCO<sub>2</sub> category x treatment group (High or Low SpO<sub>2</sub>) was significant for Fluctuators

**Table 3: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of NDI/death**

<b>PaCO<sub>2</sub> Variable</b>	<b>Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.38 (1.25-1.52)	<.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	1.03 (0.69-1.53)	0.90
<b>Hypercapnic</b>	2.69 (1.82-3.96)	<.0001
<b>Fluctuator</b>	3.07 (1.84-5.12)	<.0001
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.44 (1.09-1.90)	.0093

**Table 4: Adjusted results for PaCO<sub>2</sub> variables in relation to outcome of death before discharge**

<b>PaCO<sub>2</sub> Variable</b>	<b>Odds Ratio (95% CI)</b>	<b>p-value</b>
<b>Max PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.36 (1.22-1.51)	<.0001
<b>PaCO<sub>2</sub> Category:</b>		
<b>Hypocapnic</b>	0.90 (0.54-1.50)	0.070
<b>Hypercapnic</b>	2.47 (1.61-3.77)	<.0001
<b>Fluctuator</b>	1.88 (1.03-3.43)	.0391
<b>Normocapnic</b>	REFERENCE	-
<b>Time weighted PaCO<sub>2</sub></b> <b>(per 10 mm Hg)</b>	1.28 (0.94-1.74)	0.12

## **Supplemental Tables**

**Supplemental Tables:**

**Table 1- Bivariate analyses for Severe IVH, and for Death or Severe IVH**

<b>Characteristic</b>		<b>Severe IVH (N=164)</b>	<b>No Severe IVH (N=1106)</b>	<b>p-value<sup>1</sup></b>	<b>Death or Severe IVH (N=335)</b>	<b>No Death or Severe IVH (N=979)</b>	<b>p-value<sup>1</sup></b>
<b>PaCO<sub>2</sub>, minimum level</b>	<b>#</b>	163	1098		325	971	
	<b>Mean (SD)</b>	31.8 (7)	33.6 (6.7)		34.9 (13.4)	33.6 (6.6)	
	<b>Median, IQR</b>	32 (27-37)	34 (29-38)	.0047	33 (28-38)	34 (30-38)	.69
<b>PaCO<sub>2</sub>, maximum level</b>	<b>#</b>	163	1098		325	971	
	<b>Mean (SD)</b>	76.3 (19.8)	66.7 (17)		78.6 (21.8)	65 (15.9)	
	<b>Median, IQR</b>	75 (63-85)	65.5 (55-75)	<.0001	76 (65-88)	64 (54-74)	<.0001
<b>PaCO<sub>2</sub>, standard deviation</b>	<b>#</b>	163	1077		314	951	
	<b>Mean (SD)</b>	10.9 (4.2)	9 (3.7)		12 (6.3)	8.6 (3.4)	
	<b>Median, IQR</b>	10.5 (8.1-12.7)	8.8 (6.6-10.9)	<.0001	10.6 (8.7-13.8)	8.5 (6.5-10.5)	<.0001
<b>PaCO<sub>2</sub>, time-weighted</b>	<b>#</b>	163	1098		325	971	
	<b>Mean (SD)</b>	49.6 (6.5)	48 (7.1)		52.3 (11.8)	47.5 (7.0)	
	<b>Median, IQR</b>	49.4 (45.8-54.2)	48.6 (43.6-52.9)	.0088	51.3 (46.4-55.9)	48.0 (42.8-52.5)	<.0001
<b>PaCO<sub>2</sub> category:</b>	<b>#</b>	163	1098		325	971	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Hypocapnic	# (%)	30 (18.4)	205 (18.7)	<.0001	48 (14.8)	189 (19.5)	<.0001
Hypercapnic		42 (25.8)	168 (15.3)		102 (31.4)	127 (13.1)	
Fluctuator		26 (16.0)	70 (6.4)		45 (13.9)	52 (5.4)	
Normocapnic		65(39.9)	655 (59.7)		130 (40.0)	603 (62.1)	
Treatment: CPAP or Surfactant group	#	164	1106		335	979	
	CPAP, # (%)	92 (56.1)	550 (49.7)	.13	166 (49.6)	496 (50.7)	.73
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	164	1106		335	979	
	High O <sub>2</sub> , # (%)	81 (49.4)	559 (50.5)	.78	156 (46.6)	505 (51.6)	.11
Median SpO <sub>2</sub> DOL 1-14	#	135	922		274	808	
	Mean (SD)	92.8 (2.1)	93 (2.4)		91.3 (5.2)	93.3 (2.1)	
	Median (IQR)	93 (91-94)	93 (92-94)	0.11	93 (91-94)	93 (92-94)	<.0001
Birth Weight (g)	#	164	1106		335	979	
	Mean (SD)	802 (182)	838 (193)		763 (187)	853 (190)	
	Median (IQR)	783 (681-944)	830 (700-974)	.03	750 (640-881)	850 (710-990)	<.0001
Gender	#	164	1106		335	979	
	Male, # (%)	99 (60.4)	588 (53.2)	.08	197 (58.8)	514 (52.5)	.046
Race:	# (%)			.016			.092
NH Black		55 (33.5)	421 (38.1)		112 (33.4)	376 (38.4)	
NH White		55 (33.5)	442 (40.0)		133 (39.7)	387 (39.5)	
Hispanic		44 (26.8)	208 (18.8)		72 (21.5)	187 (19.1)	
Other		10 (6.1)	35 (3.2)		18 (5.4)	29 (3.0)	

Characteristic		Severe IVH (N=164)	No Severe IVH (N=1106)	p-value <sup>1</sup>	Death or Severe IVH (N=335)	No Death or Severe IVH (N=979)	p-value <sup>1</sup>
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	55 (33.5)	421 (38.1)	.26	112 (33.4)	376 (38.4)	.104
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	55 (33.5)	442 (40.0)	.12	133 (39.7)	387 (39.5)	.96
HTN, pregnancy induced	#	155	1041		317	920	
	Yes, # (%)	9 (5.8)	121 (11.6)	.03	21 (6.6)	110 (12.0)	.0078
Rupture of membranes > 24 hours prior to birth	#	160	1083		319	964	
	Yes, # (%)	38 (23.8)	376(34.7)	.006	97 (30.4)	336 (34.9)	.15
Prenatal steroids	#	164	1105		334	979	
	Yes, # (%)	158 (96.3)	1061 (96.0)	.84	325 (97.3)	938 (95.8)	.22
1 minute Apgar < 3	#	164	1105		334	978	
	Yes, # (%)	49 (29.9)	241 (21.8)	.022	120 (35.9)	200 (20.4)	<.0001
5 minute Apgar < 3	#	164	1106		335	979	
	Yes, # (%)	10 (6.1)	33 (3.0)	.04	29 (8.7)	29 (3.0)	<.0001
Prophylactic indomethacin	#	164	1106		309	979	
	Yes, # (%)	60 (36.6)	437 (39.5)	.47	117 (37.9)	384 (39.2)	.67
Vaginal delivery	#	164	1106		335	979	
	Yes, # (%)	57 (34.8)	367 (33.2)	.69	108 (32.2)	325 (33.2)	.74

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 2 - Bivariate analyses for BPD (in subset of survivors to 36 weeks) and Death or BPD (in all infants)

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	441	659		639	659	
	Mean (SD)	32.8 (6.6)	33.8 (6.6)		34.1 (10.6)	33.8 (6.6)	
	Median, IQR	33 (29-37)	34 (30-38)	.015	33 (29-38)	34 (30-38)	.25
PaCO <sub>2</sub> , maximum level	#	441	659		639	659	
	Mean (SD)	74 (16)	61.2 (15.2)		75.9 (18.7)	61.2 (15.2)	
	Median, IQR	72 (64-83)	60 (50-69)	<.0001	73 (65-85)	60 (50-69)	<.0001
PaCO <sub>2</sub> , standard deviation	#	438	642		625	642	
	Mean (SD)	10 (3.2)	8.1 (3.3)		10.9 (5.1)	8.1 (3.3)	
	Median, IQR	9.8 (7.8-11.8)	8.0(5.7-9.9)	<.0001	10.2 (8.1-12.7)	8 (5.7-9.9)	<.0001
PaCO <sub>2</sub> , time-weighted	#	441	659		639	659	
	Mean (SD)	50.7 (6.2)	45.8 (6.8)		51.7 (9.4)	45.8 (6.8)	
	Median, IQR	51 (47.3-54.3)	46.2 (41.1-50.4)	<.0001	51.2 (47.2-55.2)	46.2 (41.1-50.4)	<.0001
PaCO <sub>2</sub> category:	#	441	659		639	659	
Hypocapnic Hypercapnic Fluctuator Normocapnic	# (%)	78 (17.7)	138 (20.9)	<.0001	100 (15.7)	138 (20.9)	<.0001
		101 (22.9)	59 (9.0)		170 (26.6)	59 (9)	
		48 (10.9)	24 (3.6)		74 (11.6)	24 (3.6)	
		214 (46.5)	438 (66.5)		295 (46.2)	438 (66.5)	
Treatment: CPAP or Surfactant group	#	442	666		650	666	
	CPAP, # (%)	223 (50.4)	346 (52)	.62	317 (48.8)	346 (52.0)	.25

Characteristic		BPD (N=442)	No BPD (N=666)	p- value <sup>1</sup>	Death or BPD (N=650)	No Death or BPD (N=666)	p- value <sup>1</sup>
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	442	666		650	666	
	High O <sub>2</sub> , # (%)	237 (53.6)	331 (49.7)	.20	331 (50.9)	331 (49.7)	.66
Median SpO <sub>2</sub> DOL 1-14	#	382	529		555	529	
	Mean (SD)	92.8 (1.9)	93.6 (2.2)	<.0001	92 (3.9)	93.6 (2.2)	
	Median (IQR)	93 (91-94)	94 (92-95)		93 (91-94)	94 (92-95)	<.0001
Birth Weight (g)	#	442	666		650	666	
	Mean (SD)	769 (177)	898 (181)		760 (180)	898 (181)	
	Median (IQR)	750 (650- 870)	900 (770- 1020)	<.0001	740 (643-870)	900 (770- 1020)	<.0001
Gender	#	442	666		650	666	
	Male, # (%)	251 (56.8)	337 (50.6)	.043	375 (57.7)	337 (50.6)	.0098
Race:	# (%)						
NH Black		157 (35.5)	268 (40.2)	.013	221 (34)	268 (40.2)	.024
NH White		200 (45.3)	237 (35.6)		284 (43.7)	237 (35.6)	
Hispanic		73 (16.5)	137 (20.6)		122 (18.8)	137 (20.6)	
Other		12 (2.7)	24 (3.6)		23 (3.5)	24 (3.6)	
Race, collapsed: NH Black vs. all other races	Non- Hispanic Black, # (%)	157 (35.5)	268 (40.2)	.11	221 (34)	268 (40.2)	.019
Race, collapsed: NH White vs. all other races	Non- Hispanic White, # (%)	200 (45.3)	237 (35.6)	.0013	284 (43.7)	237 (35.6)	.0026
HTN, pregnancy induced	#	415	624		615	624	
	Yes, # (%)	53 (12.8)	63 (10.1)	.18	68 (11.1)	63 (10.1)	.58
Rupture of membranes > 24 hours prior to birth	#	431	659		626	659	
	Yes, # (%)	140 (32.5)	233 (35.4)	0.33	201 (32.1)	233 (35.4)	.22
Prenatal steroids	#	442	666		649	666	

<b>Characteristic</b>		<b>BPD (N=442)</b>	<b>No BPD (N=666)</b>	<b>p- value<sup>1</sup></b>	<b>Death or BPD (N=650)</b>	<b>No Death or BPD (N=666)</b>	<b>p- value<sup>1</sup></b>
	Yes, # (%)	427 (96.6)	636 (95.5)	.36	629 (96.9)	636 (95.5)	.18
<b>1 minute Apgar &lt; 3</b>	#	442	665		649	665	
	Yes, # (%)	124 (28.1)	114 (17.1)	<.0001	207 (31.9)	114 (17.1)	<.0001
<b>5 minute Apgar &lt; 3</b>	#	442	666		650	666	
	Yes, # (%)	19 (4.3)	17 (2.6)	.11	41 (6.3)	17 (2.6)	.0009
<b>Prophylactic indomethacin</b>	#	442	666		624	666	
	Yes, # (%)	169 (38.2)	261 (39.2)	.75	240 (38.5)	261 (39.2)	.79
<b>Vaginal delivery</b>	#	442	666		650	666	
	Yes, # (%)	123 (27.8)	240( 36.0)	.0044	193 (29.7)	240 (36.0)	.014

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 3 Bivariate analyses for NDI (in survivors) and Death or NDI (in all infants).

Characteristic		NDI (N= 98)	No NDI (N= 878)	p- value <sup>1</sup>	Death or NDI (N=356)	No Death or NDI (N=878)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	98	872		346	872	
	Mean (SD)	31.3 (7.0)	33.6 (6.6)		34.9 (13.1)	33.6 (6.6)	
	Median, IQR	31 (26-36)	33 (30-38)	.0013	33 (28-38)	33 (30-38)	0.95
PaCO <sub>2</sub> , maximum level	#	98	872		346	872	
	Mean (SD)	75.2 (19.6)	64.8 (16)		78.7 (21.4)	64.8 (16.0)	
	Median, IQR	74 (65-88)	64 (54-74)	<.0001	76 (66-88)	64 (54-74)	<.0001
PaCO <sub>2</sub> , standard deviation	#	98	853		335	853	
	Mean (SD)	10.2 (3.6)	8.6 (3.4)		11.9 (6.2)	8.6 (3.4)	
	Median, IQR	10.0 (8-12.5)	8.5 (6.5-10.5)	<.0001	10.5 (8.8-13.7)	8.5 (6.5-10.5)	<.0001
PaCO <sub>2</sub> , time-weighted	#	98	872		346	872	
	Mean (SD)	49.7 (7.3)	47.4 (6.9)		52.5 (11.6)	47.4 (6.9)	
	Median, IQR	49.6 (46.6-54.6)	48 (42.8-52.3)	.0014	51.7 (47.1-56)	48 (42.8-52.3)	<.0001
PaCO <sub>2</sub> category:	#	98	872		346	872	
Hypocapnic	# (%)	22 (22.5)	171 (19.6)	<.0001	51 (14.7)	171 (19.6)	<.0001
Hypercapnic		25 (25.5)	111 (12.7)		111 (32.1)	111 (12.7)	
Fluctuator		17 (17.4)	44 (5.1)		49 (14.2)	44 (5.1)	
Normocapnic		34 (34.7)	546 (62.6)		135 (39.0)	546 (62.6)	
Treatment: CPAP or Surfactant group	#	98	878		356	878	
	CPAP, # (%)	55 (56.1)	448 (51.0)	0.34	173 (48.6)	448 (51.0)	0.44

<b>Characteristic</b>		<b>NDI (N= 98)</b>	<b>No NDI (N= 878)</b>	<b>p- value<sup>1</sup></b>	<b>Death or NDI (N=356)</b>	<b>No Death or NDI (N=878)</b>	<b>p-value<sup>1</sup></b>
<b>Treatment: SpO<sub>2</sub> group, High or Low O<sub>2</sub></b>	#	98	878		356	878	
	High O <sub>2</sub> , # (%)	53 (54.1)	451 (51.4)	0.61	171 (48)	451 (51.4)	0.29
<b>Median SpO<sub>2</sub> DOL 1-14</b>	#	80	721		294	721	
	Mean (SD)	92.9 (1.7)	93.3 (2.1)		91.3 (5.0)	93.3 (2.1)	
	Median (IQR)	93 (92- 94)	93 (92-94)	0.18	93 (91.94)	93 (92-94)	<.0001
<b>Birth Weight (g)</b>	#	98	878		356	878	
	Mean (SD)	774 (192)	859 (187)		746 (185)	859 (187)	
	Median (IQR)	754 (643- 914)	850 (710- 995)	<.0001	734 (621- 870)	850 (710- 995)	<.0001
<b>Gender</b>	#	98	878		356	878	
	Male, # (%)	58 (59.2)	457 (52.1)	0.18	213 (59.8)	457 (52.1)	.013
<b>Race:</b>	# (%)						
NH Black		37 (37.8)	333 (37.9)	0.89	125 (35.1)	333 (37.9)	0.47
NH White		37 (37.8)	354 (40.3)		139 (39)	354 (40.3)	
Hispanic		21 (21.4)	161 (18.3)		78 (21.9)	161 (18.3)	
Other		3 (3.1)	30 (3.4)		14 (3.9)	30 (3.4)	
<b>Race, collapsed: NH Black vs. all other races</b>	Non-Hispanic Black, # (%)	37 (37.8)	333 (37.9)	0.97	125 (35.1)	333 (37.9)	0.35
<b>Race, collapsed: NH White vs. all other races</b>	Non-Hispanic White, # (%)	37 (37.8)	354 (40.3)	0.62	139 (39)	354 (40.3)	0.68
<b>HTN, pregnancy induced</b>	#	88	829		335	829	
	Yes, # (%)	9 (10.2)	99 (11.9)	0.64	28 (8.4)	99 (11.9)	.08
<b>Rupture of membranes &gt; 24 hours prior to birth</b>	#	97	863		341	863	
	Yes, # (%)	26 ( 26.8)	300 (34.8)	0.12	104 (30.5)	300 (34.8)	0.16

<b>Characteristic</b>		<b>NDI (N= 98)</b>	<b>No NDI (N= 878)</b>	<b>p- value<sup>1</sup></b>	<b>Death or NDI (N=356)</b>	<b>No Death or NDI (N=878)</b>	<b>p-value<sup>1</sup></b>
<b>Prenatal steroids</b>	<b>#</b>	98	878		355	878	
	<b>Yes, # (%)</b>	96 (98.0)	839 (95.6)	0.26	346 (97.5)	839 (95.6)	0.12
<b>1 minute Apgar &lt; 3</b>	<b>#</b>	98	877		355	877	
	<b>Yes, # (%)</b>	36 (36.7)	181 (20.6)	.0003	130 (36.6)	181 (20.6)	<.0001
<b>5 minute Apgar &lt; 3</b>	<b>#</b>	98	878		356	878	
	<b>Yes, # (%)</b>	7 (7.1)	27 (3.1)	.037	29 (8.2)	27 (3.1)	.0001
<b>Prophylactic indomethacin</b>	<b>#</b>	98	878		330	878	
	<b>Yes, # (%)</b>	37 (37.8)	336 (38.3)	0.92	131 (39.7)	336 (38.3)	0.65
<b>Vaginal delivery</b>	<b>#</b>	98	878		356	878	
	<b>Yes, # (%)</b>	29 (29.6)	289 (32.9)	0.51	114 (32)	289 (32.9)	0.76

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

Table 4 Bivariate analyses for Death

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
PaCO <sub>2</sub> , minimum level	#	227	991	
	Mean (SD)	36.6 (15.2)	33.4 (6.6)	
	Median, IQR	35 (30-39)	33 (29-38)	.026
PaCO <sub>2</sub> , maximum level	#	227	991	
	Mean (SD)	80.8 (22.4)	66 (16.7)	
	Median, IQR	77 (67-91)	65 (54-75)	<.0001
PaCO <sub>2</sub> , standard deviation	#	216	972	
	Mean (SD)	12.9 (7.1)	8.8 (3.4)	
	Median, IQR	11.3 (9.2-14.9)	8.7 (6.6-10.7)	<.0001
PaCO <sub>2</sub> , time-weighted	#	227	991	
	Mean (SD)	53.9 (13.1)	47.7 (7.0)	
	Median, IQR	52.4 (47.6-56.5)	48.2 (43.2-52.7)	<.0001
PaCO <sub>2</sub> category:	#	227	991	
Hypocapnic	# (%)	26 (11.5)	196 (19.8)	<.0001
Hypercapnic		82 (36.1)	140 (14.1)	
Fluctuator		29 (12.8)	64 (6.5)	
Normocapnic		90 (39.7)	591 (59.6)	
Treatment: CPAP or Surfactant group	#	237	997	
	CPAP, # (%)	109 (46)	512 (51.4)	0.14
Treatment: SpO <sub>2</sub> group, High or Low O <sub>2</sub>	#	237	997	
	High O <sub>2</sub> , # (%)	107 (45.2)	515 (51.7)	.07
Median SpO <sub>2</sub> DOL 1-14	#	197	818	
	Mean (SD)	90.5 (5.8)	93.2 (2.1)	
	Median (IQR)	92 (90-94)	93 (92-94)	<.0001
Birth Weight (g)	#	237	997	
	Mean (SD)	735 (184)	848 (189)	
	Median (IQR)	720 (610-860)	840 (710-986)	<.0001

Characteristic		Death (N=237)	No Death (N=997)	p-value <sup>1</sup>
Gender	#	237	997	
	Male, # (%)	144 (60.8)	526 (52.8)	.026
Race:	# (%)			
NH Black		77(32.5)	381 (38.2)	0.26
NH White		96 (40.5)	397 (39.8)	
Hispanic		53 (22.4)	186 (18.7)	
Other		11 (4.6)	33 (3.3)	
Race, collapsed: NH Black vs. all other races	Non-Hispanic Black, # (%)	77 (32.5)	381 (38.2)	0.10
Race, collapsed: NH White vs. all other races	Non-Hispanic White, # (%)	96 (40.5)	397 (39.8)	0.85
HTN, pregnancy induced	#	226	938	
	Yes, # (%)	16 (7.1)	111 (11.8)	0.04
Rupture of membranes > 24 hours prior to birth	#	224	980	
	Yes, # (%)	72 (32.1)	332 (33.9)	0.62
Prenatal steroids	#	236	997	
	Yes, # (%)	7 (3)	41 (4.1)	0.41
1 minute Apgar < 3	#	236	996	
	Yes, # (%)	90 (38.1)	221 (22.2)	<.0001
5 minute Apgar < 3	#	237	997	
	Yes, # (%)	22 (9.3)	34 (3.4)	<.0001
Prophylactic indomethacin	#	211	997	
	Yes, # (%)	83 (39.3)	384 (38.5)	0.82
Vaginal delivery	#	237	997	
	Yes, # (%)	77 (32.5)	326 (32.7)	0.95

<sup>1</sup> p-values from Wilcoxon tests for continuous variables and Chi Square tests for categorical variables

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**Cc:** michael.cotten@duke.edu; Archer, Stephanie (NIH/NICHD) [E]; jgabrio@rti.org; kzaterka@rti.org; mcunningham@rti.org; petrie@rti.org  
**Subject:** Re: OHRP public meeting.  
**Date:** Saturday, July 27, 2013 4:33:53 PM

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FYI, Erika received the following email from OHRP:

Dear Dr. Fernandez,

There is no registration to participate in the Public Meeting via live streaming technology. For participants who cannot attend the public meeting in person there will be an option to view the public meeting via live streaming technology. Information on the option to view the meeting via live streaming technology will be posted at a later time on the OHRP website at <http://www.hhs.gov/ohrp>. Any other updates to information on the meeting will be posted on the OHRP website. A list serv announcement may also be sent out with information regarding the live streaming option.

>>> "Wally Carlo, M.D." 07/27/13 2:20 PM >>>

Mike just confirmed that Rob Califf will be at the meeting.

Wally

-----Original message-----

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

To: " (suhas.kallapur@cchmc.org) ", "Abbot Laptook (alaptook@wihri.org) ", "Abhik Das (adas@rti.org) ", "Ambal (ambal@uab.edu) ", "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu) ", "barbara\_stoll@oz.ped.emory.edu" , "bpindex@iupui.edu" , "carl\_dangio@umc.rochester.edu" , "Carlton, David P" , "cotte010@mc.duke.edu" , "dstevenson@stanford.edu" , "dwallace@rti.org" , "Ed Bell (edward-bell@uiowa.edu) ", "goldb008@mc.duke.edu" , "Greg Sokol (gsokol@iupui.edu) ", "Haresh Kirpalani (KIRPALANIH@email.chop.edu) ", John Barks , "Jon.E.Tyson@uth.tmc.edu" , "Kennedy, Kathleen A" , "Krisa Van Meurs (vanmeurs@stanford.edu) ", "Kristi Watterberg (kwatterberg@salud.unm.edu) ", "Kurt Schibler [kurt.schibler@cchmc.org] ", "Luc Brion (luc.brion@utsouthwestern.edu) ", "Martin Keszler (mkeszler@wihri.org) ", "mcw3@po.cwru.edu" , "Meena Garg (mgarg@mednet.ucla.edu) ", "Nelin, Leif" , "Pablo.Sanchez@UTSouthwestern.edu" , "Polin, Richard" , "Robin Ohls (rohls@salud.unm.edu) ", "ronnie\_guillet@umc.rochester.edu" , Satyan Lakshminrusimha , "Schmidt, Barbara (Neonatology) ", "Seetha Shankaran" , "Sood, Beena [bsood@med.wayne.edu] ", "Truog, William (MD)" ,

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Cc: "Archer, Stephanie (NIH/NICHD) [E]" , " (mcunningham@rti.org)" , " (kzaterka@rti.org)" , "Petrie, Carolyn" ,  
"Jenna Gabrio (jgabrio@rti.org)"  
Sent: Thu, Jul 25, 2013 18:38:52 GMT+00:00  
Subject: Most recent cooling for HIE meta analysis link

Here is the link for the most recent Cochrane meta analysis-  
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003311.pub3/pdf>

From page 23:  
Implications for research

Further well-designed and executed studies with appropriate power are required to determine the optimal modality  
(head versus bod

**From:** Gantz, Marie  
**To:** Walsh, Michele; Finer, Neil; Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Friday, July 26, 2013 12:32:43 PM

---

Thanks, Michele. That is helpful.

Marie Gantz, Ph.D.  
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-----Original Message-----

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Friday, July 26, 2013 11:34 AM  
**To:** Finer, Neil; Wally Carlo, M.D.  
**Cc:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

I used the NRN BPD calculator with the following test case: 27wk male 850gm (which I picked as the mean from SUPPORT) and two different situations:

40%, vent-

40%, cpap-

at day 1,3,7 and 14 days of life.

For vent: prediction of death or mod/severe bpd-- exceeded 57%. (57% at day 1-73% at day 14)

For cpap: prediction of death or mod/severe bpd exceeded 49.6% (49.6% at day 1- 58% at day 14) I believe that this type of data could be used to justify the definition of severity.

Look forward to your thoughts.

Michele

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**From:** Walsh, Michele  
**Sent:** Wednesday, July 24, 2013 4:40 PM  
**To:** Finer, Neil; Wally Carlo, M.D.  
**Cc:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; adas@rti.org  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Perhaps put it in the BPD calculator and see What the predicted severe BPD rate is.

Michele Walsh  
Chief Division of Neonatology  
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Professor of Pediatrics  
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-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Wednesday, July 24, 2013 3:43 PM  
To: Wally Carlo, M.D.  
Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele;  
Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu;  
nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; adas@rti.org  
Subject: Re: SUPPORT ROP/SpO2 secondary paper

Hi Marie

The important part was the consecutive 8 hours as this is nowadays unusual I am not an expert and this was a clinically based definition It has not been validated perhaps till now Thanks to you Neil

my iPhone

On Jul 24, 2013, at 12:08 PM, "Wally Carlo, M.D."  
<WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>> wrote:

Marie.

It is based on expert opinion. Neil is the expert. I think he recommended it and we used it.

Wally

-----Original message-----

From: "Gantz, Marie" <mgantz@rti.org<mailto:mgantz@rti.org>>  
To: "Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Wally Carlo,  
M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>, "Walsh,  
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<adas@rti.org<mailto:adas@rti.org>>  
Sent: Wed, Jul 24, 2013 14:49:38 GMT+00:00  
Subject: RE: SUPPORT ROP/SpO2 secondary paper

Thanks, everyone, for your comments so far. As Wally noted, the definition of severe illness (FiO2 > 0.4 and > 8hrs of mechanical ventilation in first 15 days) came from the SUPPORT subcommittee members. Neil and Wally, can you provide insight into why this particular definition was chosen?

Marie

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919-597-5110

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Wednesday, July 24, 2013 8:51 AM  
To: 'Wally Carlo, M.D.'; Walsh, Michele; Gantz, Marie;  
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Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik  
Subject: RE: SUPPORT ROP/SpO2 secondary paper

I added my comments with Wally's and Michele's Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Wednesday, July 24, 2013 8:28 AM  
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Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>;  
nxs5@case.edu<mailto:nxs5@case.edu>;  
ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>;  
Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik;  
Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT ROP/SpO2 secondary paper

I have added my comments to those of Michele. I think Michele raises very important points.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
1700 6th Avenue South  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Susan Hintz"  
**Cc:** "alexis.davis@stanford.edu"; "(mcunningham@rti.org)"; "(kzaterka@rti.org)"  
**Subject:** RE: running ahead  
**Date:** Friday, July 26, 2013 11:46:12 AM

---

We are running ahead –you will probably go at 115-130 PM- Kristi will be out by 2

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Susan Hintz [mailto:[srhintz@stanford.edu](mailto:srhintz@stanford.edu)]  
**Sent:** Friday, July 26, 2013 11:44 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** alexis.davis@stanford.edu; (mcunningham@rti.org); (kzaterka@rti.org)  
**Subject:** Re: running ahead

To clarify -  
SUPPORT with Finer and Carlo at 12:45 ET -

SUPPORT school age follow up - I know that Kristi needs to get out by (I think) 2, so in terms of whether School Age Follow Up goes next or Alexis goes next after SUPPORT, that will be up to Kristi and her schedule. Either fine with me -

Susan

On Jul 26, 2013, at 8:15 AM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

SUPPORT discussion will occur at 1245 PM – alexis can follow, then you

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909

301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Susan Hintz [mailto:[srhintz@stanford.edu](mailto:srhintz@stanford.edu)]  
**Sent:** Friday, July 26, 2013 11:10 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** ([mcunningham@rti.org](mailto:mcunningham@rti.org)); ([kzaterka@rti.org](mailto:kzaterka@rti.org))  
**Subject:** Re: running ahead

Yes - could join earlier. When?

What about Alexis?

Sent from my iPhone

On Jul 26, 2013, at 7:00 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

We are running ahead and will keep you posted – can you join before 1 PM ET?

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research  
Network  
Pregnancy and Perinatology Branch  
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For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Roger Faix  
**To:** Gantz, Marie; Wally Carlo, M.D.; Finer, Neil  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Rich, Wade; Bradley Yoder; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Friday, July 26, 2013 10:42:43 AM

---

Hi All!

I think we should explain why we included 'illness severity' as a factor and how we decided to use the particular index chosen. That will help the reviewers and readers, I believe. I vote for leaving 'illness' severity in.

Roger

---

**From:** Gantz, Marie [mgantz@rti.org]  
**Sent:** Friday, July 26, 2013 8:35 AM  
**To:** Wally Carlo, M.D.; Finer, Neil  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Rich, Wade; Roger Faix; Bradley Yoder; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Actually, we did not define the severe illness variable until after the primary papers. There seems to be some disagreement about whether we can justify the current definition of severe illness in the paper. Does anyone else want to weigh in?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
919-597-5110

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

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, July 26, 2013 10:22 AM  
**To:** Finer, Neil; Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

I agree to keep it in. We put it in the main paper already and the reviewers did not raise problems with it

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

**From:** Finer, Neil [mailto:finer@ucsd.edu]  
**Sent:** Friday, July 26, 2013 9:18 AM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Hi Marie  
I am OK with keeping it

Neil

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

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Friday, July 26, 2013 7:07 AM  
To: Finer, Neil  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Rich, Wade;  
ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org;  
Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
Subject: RE: SUPPORT ROP/SpO2 secondary paper

...although I should clarify about what your response really meant. Do you think it is reasonable to drop the severe illness variable?

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
919-597-5110

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

From: Gantz, Marie  
Sent: Friday, July 26, 2013 10:05 AM  
To: 'Finer, Neil'  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Rich, Wade;  
ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org;  
Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
Subject: RE: SUPPORT ROP/SpO2 secondary paper

Thanks, Neil. With that in mind, I will look at dropping the severe illness variable from the analysis.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
919-597-5110

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Thursday, July 25, 2013 2:57 PM  
To: Gantz, Marie  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh, Michele; Rich, Wade;  
ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org;  
Kurt.Schibler@cchmc.org; Das, Abhik; Timothy Stevens  
Subject: Re: SUPPORT ROP/SpO2 secondary paper

Hi Marie

I do not think that needs to be done - especially for your paper The NRN may want to explore various other indices and see which performs best In addition it may be something Tim and you could look at for the Breathing outcomes Study Neil

On 7/25/13 11:35 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

>My recollection was that the indicator of illness was to help  
>differentiate between low sats that were due to illness and low sats  
>that were due to targeting. We used it in the models to predict ROP,  
>along with other morbidities (NEC, IVH, etc.), time on oxygen, and  
>percent of time in specific saturation ranges. Do you think it is  
>necessary to try to control for illness beyond the specific morbidities  
>that are already in the models? If so, should we consider a different indicator of illness?

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org

>919-597-5110

>

>-----Original Message-----

>From: Finer, Neil [mailto:nfiner@ucsd.edu]

>Sent: Wednesday, July 24, 2013 10:56 AM

>To: Gantz, Marie

>Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Walsh,

>Michele; Rich, Wade; ROGER.FAIX@HSC.UTAH.EDU;

>Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org;

>Kurt.Schibler@cchmc.org; Das, Abhik

>Subject: Re: SUPPORT ROP/SpO2 secondary paper

>

>I think we must have been trying to separate these infants in an  
>attempt to see if they had different outcomes Used over a 15 day  
>period, I am not sure how useful this definition is as I now look at it  
>Perhaps Wally can shed further light on this Neil

>

>On Jul 24, 2013, at 7:49 AM, "Gantz, Marie"

><mgantz@rti.org<mailto:mgantz@rti.org>> wrote:

>

>Thanks, everyone, for your comments so far. As Wally noted, the  
>definition of severe illness (FiO2 > 0.4 and > 8hrs of mechanical  
>ventilation in first 15 days) came from the SUPPORT subcommittee members.  
>Neil and Wally, can you provide insight into why this particular  
>definition was chosen?

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org<mailto:mgantz@rti.org>

>919-597-5110

>

>From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

>Sent: Wednesday, July 24, 2013 8:51 AM

>To: 'Wally Carlo, M.D.'; Walsh, Michele; Gantz, Marie;

>nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>;

>wrich@ucsd.edu<mailto:wrich@ucsd.edu>;

>ROGER.FAIX@HSC.UTAH.EDU<mailto:ROGER.FAIX@HSC.UTAH.EDU>;

>Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>;

>nxs5@case.edu<mailto:nxs5@case.edu>;  
>ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>;  
>Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik  
>Subject: RE: SUPPORT ROP/SpO2 secondary paper  
>  
>I added my comments with Wally's and Michele's Rose  
>  
>Rosemary D. Higgins, MD  
>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal  
>Research Network Pregnancy and Perinatology Branch NIH  
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>Bethesda, MD 20892  
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>301-496-5575  
>301-496-3790 (FAX)  
>higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>  
>  
>From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
>Sent: Wednesday, July 24, 2013 8:28 AM  
>To: Walsh, Michele; Gantz, Marie;  
>nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>;  
>wrich@ucsd.edu<mailto:wrich@ucsd.edu>;  
>ROGER.FAIX@HSC.UTAH.EDU<mailto:ROGER.FAIX@HSC.UTAH.EDU>;  
>Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>;  
>nxs5@case.edu<mailto:nxs5@case.edu>;  
>ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>;  
>Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik;  
>Higgins, Rosemary (NIH/NICHD) [E]  
>Subject: RE: SUPPORT ROP/SpO2 secondary paper  
>  
>I have added my comments to those of Michele. I think Michele raises  
>very important points.  
>  
>Wally  
>  
>Wally Carlo, M.D.  
>Edwin M. Dixon Professor of Pediatrics  
>University of Alabama at Birmingham  
>Director, Division of Neonatology  
>Director, Newborn Nurseries  
>1700 6th Avenue South  
>176F Suite 9380R  
>Birmingham, AL 35233-7335  
>Phone: 205 934 4680  
>FAX: 205 934 3100  
>Cell: 205 266 4004  
>  
>From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
>Sent: Tuesday, July 23, 2013 3:29 PM  
>To: Gantz, Marie; Wally Carlo, M.D.;  
>nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>;  
>wrich@ucsd.edu<mailto:wrich@ucsd.edu>;  
>ROGER.FAIX@HSC.UTAH.EDU<mailto:ROGER.FAIX@HSC.UTAH.EDU>;  
>Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>;  
>nxs5@case.edu<mailto:nxs5@case.edu>;

>ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>;  
>Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik;  
>higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>  
>Subject: RE: SUPPORT ROP/SpO2 secondary paper  
>  
>Overall: given the current environment, I think we need to be  
>extremely careful in the wording of this paper and Of the growth  
>secondary. I have edited language with this cautious lens.  
>  
>I have embedded comments in track change.  
>1. Some of the terminology could be altered to improve understanding  
>For  
>example: timepoint of outcome determination: <sup>3</sup>36wks PMA or severe ROP  
>determination<sup>2</sup> Leads to long sentences with the phrase severe ROP three  
>times. Suggest instead <sup>3</sup>36wks PMA or ophthalmologic determination<sup>2</sup> 2.  
>Both papers need to provide some justification for the unusual  
>definition of severe illness: FiO2 > 0.4 and > 8hrs of mechanical  
>ventilation In first 15 days. How was this determined? It will raise  
>eyebrows. I suspect it was determined by some statistical cutpoint??  
>  
>3. I do not understand Figure 2 and interpretation at all.  
> Also confused by one section in the results that references figure 2  
>and  
>states:  
><sup>3</sup>In multivariate analysis, severe ROP was most highly associated with  
>percentages of time while on supplemental oxygen with SpO2 values less  
>than 80% (correlations between the discriminant function and  
>percentages of time at SpO2 values <80% were all >0.5).<sup>2</sup> This is not  
>mentioned in the discussion and I do not understand what it means<sup>3</sup>  
>seems to contradict the results of the main trial.  
>  
>4. Can the horizontal axis in Figure 1 and Fig 3 be expanded to get the  
>full number horizontally- or maybe just list every other number.  
>  
>Michele Walsh  
>Chief Division of Neonatology  
>Rainbow Babies & Childrens Hospital  
>Professor of Pediatrics  
>Case Western Reserve University  
>11100 Euclid Avenue, Mailstop 6010  
>Cleveland, OH 44106-6010  
>email: michele.walsh@cwru.edu<mailto:michele.walsh@cwru.edu>  
>Phone: (216) 844-3387  
>Fax: (216) 844-3380  
>  
>  
>From: Gantz, Marie [mailto:mgantz@rti.org]  
>Sent: Thursday, July 11, 2013 2:26 PM  
>To: WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>;  
>nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>;  
>>wrich@ucsd.edu<mailto:wrich@ucsd.edu>;  
>ROGER.FAIX@HSC.UTAH.EDU<mailto:ROGER.FAIX@HSC.UTAH.EDU>;  
>Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>; Walsh,  
>Michele; nxs5@case.edu<mailto:nxs5@case.edu>;  
>ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>;  
>Kurt.Schibler@cchmc.org<mailto:Kurt.Schibler@cchmc.org>; Das, Abhik;  
>higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

>Subject: SUPPORT ROP/SpO2 secondary paper

>

>Hi all,

>

>Attached is a long-overdue draft of the ROP/SpO2 secondary paper for  
>SUPPORT. The target journal is J Perinatology. I would appreciate it if  
>you would review and send comments/edits by July 26. Thanks in advance.

>

>Marie

>

>Marie Gantz, Ph.D.

>Senior Research Statistician

>RTI International

>mgantz@rti.org<<mailto:mgantz@rti.org>>

>919-597-5110

>

>

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>

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>5122.31 and  
>3701.243 prohibit disclosure of this information without the specific  
>written consent of the person to whom it pertains, or as otherwise  
>permitted by law.

**From:** Roger Faix  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\*CHANGE OF TIME FOR NRN SUPPORT DISCUSSION\*\*\*\*\*  
**Date:** Friday, July 26, 2013 10:30:00 AM

---

Thanks, Rose!

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Friday, July 26, 2013 8:10 AM  
**To:** 'nfiner@ucsd.edu'; 'richard.ehrenkranz@yale.edu'; Roger Faix; Bradley Yoder; 'Duara, Shahnaz' (SDuara@med.miami.edu); 'Frantz, Ivan'; 'Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org)'; 'Michael O'Shea (moshea@wakehealth.edu)'; 'Phelps, Dale'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; ' (mcunningham@rti.org)'; 'Abhik Das (adas@rti.org)'; srhintz@stanford.edu  
**Subject:** \*\*\*\*\*CHANGE OF TIME FOR NRN SUPPORT DISCUSSION\*\*\*\*\*

Our meeting is running ahead of schedule. The SUPPORT Discussion will occur at 12:45 PM ET

Dial:  
Within the USA

(b)(6)

OR

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 8:44 AM  
**To:** nfiner@ucsd.edu; richard.ehrenkranz@yale.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Duara, Shahnaz' (SDuara@med.miami.edu); Frantz, Ivan; Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org); Michael O'Shea (moshea@wakehealth.edu); 'Phelps, Dale'

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; (mcunningham@rti.org); Abhik Das (adas@rti.org)  
**Subject:** NRN SC meeting this week

TO SUPPORT INVESTIGATORS:

I have attached the NRN SC meeting agenda for later this week. We invite you to join two discussions:

1. Thursday July 25 at 10:30 am – Dr. Hudson
2. Friday July 26 at 2 pm – SUPPORT discussion
3. For those of you who knew Dr. Korones and want to stay on the call at 11 on Thursday, you are most welcome to attend.

Let me know if you have any questions. If you are having trouble calling in, please email Meg and I.

Dial:  
Within the USA

(b)(6)

OR

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Roger Faix  
**To:** Wally Carlo, M.D.; Gantz, Marie; nfiner@ucsd.edu; wrich@ucsd.edu; Bradley Yoder; Michele.Walsh@UHhospitals.org; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Friday, July 26, 2013 10:27:58 AM

---

I agree with Wally's comment below.

Roger

---

**From:** Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
**Sent:** Friday, July 26, 2013 8:05 AM  
**To:** Gantz, Marie; Roger Faix; nfiner@ucsd.edu; wrich@ucsd.edu; Bradley Yoder; Michele.Walsh@UHhospitals.org; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; higginsr@mail.nih.gov  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Dear Co-authors:

I initially had suggested to Marie that this manuscript may be better for an intermediate impact factor paper as it is a bit technical. However, I think that this manuscript will be important as it shows that saturations slightly above the 91-95% range are not associated with ROP but in contrast, it is the long exposure to oxygen supplementation that is strongly associated with ROP together with important demographic characteristics that are associated with increased risk.

Thus, I think Pediatrics, J Peds, JAMA Peds, or Archives may be target journals.

Wally

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Friday, July 26, 2013 8:42 AM  
**To:** Roger Faix; Wally Carlo, M.D.; nfiner@ucsd.edu; wrich@ucsd.edu; Bradley Yoder; Michele.Walsh@UHhospitals.org; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; higginsr@mail.nih.gov  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Roger, those are very helpful comments. Thanks.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
mgantz@rti.org  
919-937-5110

---

**From:** Roger Faix [mailto:Roger.Faix@hsc.utah.edu]  
**Sent:** Thursday, July 25, 2013 8:16 PM

**To:** Gantz, Marie; [WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); Bradley Yoder; [Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org); [nxs5@case.edu](mailto:nxs5@case.edu); [ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); Das, Abhik; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

In addition to the comments of others, I would like to add the following comments:

- 1) In the abstract, it is not clear that the conclusion addresses what is indicated as the primary objective. Reading the entire manuscript, it is clear that the objective was addressed and that time spent at specific oxygen saturation levels and/or ranges were not as strongly associated with severe ROP in the regression analysis as other features of respiratory support (esp., %age of days on supplemental oxygen, center, GA, SGA, illness severity and late-onset sepsis or meningitis). It may be more enticing to the reader to read the whole article if the Abstract conclusions report that specific SpO2 levels were less strongly predictive of severe ROP than other factors that are then enumerated.
- 2) Again in the abstract, it may be important to note that actual SpO2 values obtained were employed in the analysis, rather than merely using saturation target group assignment. This is certainly very clear in the rest of the manuscript, but may attract more readership if it is spelled out in the abstract as well.
- 3) A demographic comparison of the infants who died versus those who survived and were included in this subgroup analysis may be useful to determine if the groups were comparable at birth/SUPPORT entry.
- 4) Page 6, paragraph 4, sentence 3: This sentence is unclear to me: '...there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in low target group, 84-87% and 95-96% in the high target group)...'
- 5) Page 11, italicized comment between paragraph 1 and 2 re: need to add more interpretation of results. Is more interpretation necessary? If so, has any candidate text been developed?
- 6) In the abstract results you refer to 'severe illness (FiO2 >0.4 and on ventilator for >8 consecutive hours in the first 14 days of life)', but in the closing paragraph of the discussion (page 12) you refer to 'severe pulmonary disease'. Are these meant to refer to same infant condition? If so, I would recommend being consistent and sticking with either 'severe illness' or 'severe pulmonary illness', but not using both.

I hope these comments are useful.

Roger

---

**From:** Gantz, Marie [[mgantz@rti.org](mailto:mgantz@rti.org)]  
**Sent:** Thursday, July 11, 2013 12:25 PM  
**To:** [WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); Roger Faix; Bradley Yoder; [Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org); [nxs5@case.edu](mailto:nxs5@case.edu); [ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); Das, Abhik; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Subject:** SUPPORT ROP/SpO2 secondary paper

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

**Marie Gantz, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
**[mgantz@rti.org](mailto:mgantz@rti.org)**  
**919-537-5110**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Jon.E.Tyson@uth.tmc.edu"; "Michele Smith (Nancy.M.Smith@uth.tmc.edu)"  
**Subject:** FW: \*\*\*\*\*CHANGE OF TIME FOR NRN SUPPORT DISCUSSION\*\*\*\*\*  
**Date:** Friday, July 26, 2013 10:18:20 AM  
**Importance:** High

---

Meant to include you – 1245 PM for SUPOPRT discussion

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, July 26, 2013 10:11 AM  
**To:** 'nfiner@ucsd.edu'; 'richard.ehrenkranz@yale.edu'; 'Roger Faix (Roger.Faix@hsc.utah.edu)'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; "Duara, Shahnaz" (SDuara@med.miami.edu); 'Frantz, Ivan'; 'Elisabeth McGowan (emcgowan@tuftsmedicalcenter.org) (emcgowan@tuftsmedicalcenter.org)'; 'Michael O'Shea (moshea@wakehealth.edu)'; 'Phelps, Dale'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; ' (mcunningham@rti.org)'; 'Abhik Das (adas@rti.org)'; srhintz@stanford.edu  
**Subject:** \*\*\*\*\*CHANGE OF TIME FOR NRN SUPPORT DISCUSSION\*\*\*\*\*  
**Importance:** High

Our meeting is running ahead of schedule. The SUPPORT Discussion will occur at 12:45 PM ET

Dial:  
Within the USA

(b)(6)

OR

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

**Pregnancy and Perinatology Branch**  
**NIH**  
**6100 Executive Blvd., Room 4B03**  
**MSC 7510**  
**Bethesda, MD 20892**  
**For overnight delivery use Rockville, MD 20852**  
**301-435-7909**  
**301-496-5575**  
**301-496-3790 (FAX)**  
**[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 8:44 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); Roger Faix ([Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)); Brad Yoder ([Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)); 'Duara, Shahnaz' ([SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)); Frantz, Ivan; Elisabeth McGowan ([emcgowan@tuftsmedicalcenter.org](mailto:emcgowan@tuftsmedicalcenter.org)); Michael O'Shea ([moshea@wakehealth.edu](mailto:moshea@wakehealth.edu)); 'Phelps, Dale'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; ([mcunningham@rti.org](mailto:mcunningham@rti.org)); Abhik Das ([adas@rti.org](mailto:adas@rti.org))  
**Subject:** NRN SC meeting this week

TO SUPPORT INVESTIGATORS:

I have attached the NRN SC meeting agenda for later this week. We invite you to join two discussions:

1. Thursday July 25 at 10:30 am – Dr. Hudson
2. Friday July 26 at 2 pm – SUPPORT discussion
3. For those of you who knew Dr. Korones and want to stay on the call at 11 on Thursday, you are most welcome to attend.

Let me know if you have any questions. If you are having trouble calling in, please email Meg and I.

Dial:

Within the USA

(b)(6)

OR

Outside the USA

(b)(6)

Then, enter Participant Passcode:

(b)(6)

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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Bethesda, MD 20892

**For overnight delivery use Rockville, MD 20852**

**301-435-7909**

**301-496-5575**

**301-496-3790 (FAX)**

**[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"  
**Cc:** "(mcunningham@rti.org)"; "Petrie, Carolyn"  
**Subject:** RE: SC meeting  
**Date:** Friday, July 26, 2013 10:08:53 AM

---

12:45 PM – I will let the other SUPPORT folks know who are not at the meeting

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Friday, July 26, 2013 10:07 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** (mcunningham@rti.org); Petrie, Carolyn  
**Subject:** RE: SC meeting

Hi Rose  
I can join now or whenever you want me to call in  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, July 26, 2013 6:39 AM  
**To:** Finer, Neil  
**Cc:** (mcunningham@rti.org); Petrie, Carolyn  
**Subject:** SC meeting

Neil  
We are running ahead on our schedule for the Steering committee meeting – what is the earliest you could join a discussion?  
Let me know  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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**301-435-7909**

**301-496-5575**

**301-496-3790 (FAX)**

**[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "Wally Carlo, M.D."  
**Cc:** "nfiner@ucsd.edu"  
**Subject:** RE: Call  
**Date:** Friday, July 26, 2013 9:40:08 AM

---

I just emailed him also – we had invited the other support investigators so once I hear from Neil we can email those folks also

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, July 26, 2013 9:39 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** nfiner@ucsd.edu  
**Subject:** Call

Hi Rose:

I emailed Neil to see if he would be available earlier. FYI.

Wally

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Tyson, Jon E"  
**Subject:** RE: part of an e mail from John Lantos to me  
**Date:** Thursday, July 25, 2013 1:49:43 PM

---

May also come up tomorrow during 2PM SUPPORT discussion – you are encouraged to join

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, July 25, 2013 1:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** part of an e mail from John Lantos to me

“ My guess would be that Public Citizen is probably rallying their grassroots supporters and will have lots of people there speaking against neonatal research and accusing SUPPORT and OHRP of dastardly things. I suspect that there will be comparatively few folks defending SUPPORT and speaking to the complexities. “

If true, do we need to vigorously rally the troops to attend?

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Tyson, Jon E"  
**Subject:** RE: part of an e mail from John Lantos to me  
**Date:** Thursday, July 25, 2013 1:49:03 PM

---

This is up to individuals. Happy to discuss

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, July 25, 2013 1:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** part of an e mail from John Lantos to me

" My guess would be that Public Citizen is probably rallying their grassroots supporters and will have lots of people there speaking against neonatal research and accusing SUPPORT and OHRP of dastardly things. I suspect that there will be comparatively few folks defending SUPPORT and speaking to the complexities. "

If true, do we need to vigorously rally the troops to attend?

**From:** Roger Faix  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: OHRP meeting  
**Date:** Thursday, July 25, 2013 11:21:08 AM

---

Many thanks!

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Thursday, July 25, 2013 9:02 AM  
**To:** Roger Faix  
**Subject:** FW: OHRP meeting

Here you go

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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6100 Executive Blvd., Room 4B03  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Thursday, July 25, 2013 11:01 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** OHRP meeting

Here's the link:

<http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/aug28public.html>

**From:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** OHRP meeting  
**Date:** Thursday, July 25, 2013 10:38:25 AM

---

Should I sign up to attend?

---

Stephanie Wilson Archer  
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** "Rich, Wade"; Kris Zaterka-Baxter  
**Cc:** Garey, Donna; Bridge, Renee; Auman, Jeanette O. (joa@rti.org); Jamie Newman (newman@rti.org); Jane Hammond (hammond@rti.org); Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Wade Rich  
**Date:** Thursday, July 25, 2013 8:53:01 AM

---

Thanks, Wade. Hope you (b)(6)

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
6100 Executive Boulevard, Room 4B03  
Rockville, MD 20852

Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Wednesday, July 24, 2013 5:29 PM  
**To:** Kris Zaterka-Baxter; Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Garey, Donna; Bridge, Renee; Auman, Jeanette O. (joa@rti.org)  
**Subject:** Wade Rich

I am retiring from UCSD effective 10/5, with a last day of September 20. Donna Garey, our PI for the network trials, will continue to work with the NICHD. She has commented to me that information sometimes goes to her, and sometimes to Yvonne Vaucher. I would request the following:

- 1) That Dr. Garey ( [dgarey@ucsd.edu](mailto:dgarey@ucsd.edu) ) receive copies of any Network related emails
- 2) That Renee Bridge ( [rbridge@ucsd.edu](mailto:rbridge@ucsd.edu) ) be the primary contact for the site.

Wade Rich, RRT, CCRC  
Clinical Research Coordinator  
Division of Neonatology  
Univ. of Calif, San Diego  
619-543-5375  
FAX 619-543-3812

**Blansfield, Earl (NIH/NICHD) [E]**

**From:** Rostkowski, Teresa <trostkowski@lchb.com>  
**Sent:** Wednesday, July 24, 2013 6:29 PM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; 'Rh298@nih.gov'  
**Cc:** Vincent, Fabrice N.; Kruse, Juliette; (b)(6)  
(b)(6)  
**Subject:** SUPPORT Study-Request for Information  
**Attachments:** (b)(6) Authorization.pdf

July 24, 2013

Via email and Fax

Rosemary Higgins, M.D.  
NICHD Neonatal Research Network  
6100 Executive Blvd Room 4B03B, MSV 7510  
Bethesda, MD 20892  
[Rh298@nih.gov](mailto:Rh298@nih.gov)

Alan Guttmacher, M.D., Director  
NICHD  
31 Center Dr. Room 2A03, MSC 2425  
Bethesda, MD 20892  
[guttmach@mail.nih.gov](mailto:guttmach@mail.nih.gov)

Re: Patient Name: (b)(6)  
Date of Birth: (b)(6)  
Date of Service: (b)(6)

Dear Dr. Higgins and Dr. Guttmacher:

Lieff Cabraser Heimann & Bernstein, LLP represents Mr. (b)(6) and his parents (b)(6) and (b)(6) in an investigation into (b)(6) participation in the SUPPORT study at the (b)(6) conducted by NICHD and (b)(6)

**We are requesting records that indicate which arm of the study group (b)(6) was assigned: low or high oxygen; surfactant and/or CPAP.** We understand from the (b)(6) (b)(6) that only the NIH has that information so please promptly produce the information; the (b)(6) previously told us that only the (b)(6) had this information and the (b)(6) says only the (b)(6) and/or NIH has the information. Please quickly release this information and related records and send any them to my attention via fax to 415-956-1008, if possible, or to my email to my attention at the above address as soon as possible. Please call me to discuss the matter at: 415-956-1000, ext. 2216.

Very truly yours,



Fabrice N. Vincent

Attachment

1110317.3

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

**Lieff  
Cabraser  
Heimann &  
Bernstein**  
Attorneys at Law

**Teresa Rostkowski**  
Paralegal  
trostkowski@lchb.com  
t 415.956.1000  
f 415.956.1008  
Lieff Cabraser Heimann & Bernstein, LLP  
275 Battery Street, 29th Floor  
San Francisco, CA 94111-3339  
www.lieffcabraser.com

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### HIPAA AUTHORIZATION FOR THE USE AND DISCLOSURE OF HEALTH INFORMATION

**PATIENT IDENTIFICATION:**

Full Legal Name: (b)(6) or Alias: \_\_\_\_\_  
Date of Birth: (b)(6) Medical Records # (SSN#): (b)(6)  
FOR INFANT: Mother's Name/SSN#: \_\_\_\_\_ Father's Name/SSN#: \_\_\_\_\_

**THIS AUTHORIZATION IS DIRECTED TO AND APPLIES TO PROTECTED HEALTH INFORMATION MAINTAINED BY: (Hospital, Physician, Medical Provider, etc.)**

- 1. (b)(6) \_\_\_\_\_
- 2. \_\_\_\_\_
- 3. \_\_\_\_\_
- 4. \_\_\_\_\_
- 5. \_\_\_\_\_
- 6. \_\_\_\_\_
- 7. \_\_\_\_\_
- 8. \_\_\_\_\_
- 9. \_\_\_\_\_
- 10. \_\_\_\_\_

Pursuant to HIPAA Standards for Privacy of Individually Identifiable Health Information, 45 C.F.R. §§ 164.512 & 164.508, I hereby authorize you to use or disclose my protected health information, as described below. I authorize the physician, healthcare providers and the company releasing my records to verbally or in writing discuss the lab results, chain of custody procedures, and clinical information related to the test with the receiving party defined below. I authorize the above-specified individuals or organizations to receive all requested health information. The purpose of the requested use or disclosure is: pending civil litigation/factual investigation. The information to be disclosed includes the following specified information:

ALL Medical Healthcare Records during approximate time period from \_\_\_\_\_ to \_\_\_\_\_ (including, but not limited to the following, specifically including information related to my identity, diagnosis, prognosis and/or treatment):

- |  |   |   |
|--|---|---|
| <input checked="" type="checkbox"/> All Inpatient Health Records   | <input checked="" type="checkbox"/> Pathology Slides  | <input checked="" type="checkbox"/> Health Record Abstract  |
| <input checked="" type="checkbox"/> All Outpatient Health Records  | <input checked="" type="checkbox"/> ER Records  | <input checked="" type="checkbox"/> Photographs, Videotapes, Images   |
| <input checked="" type="checkbox"/> Emergency Room Record  | <input checked="" type="checkbox"/> Nursing/Tech. Notes   | <input checked="" type="checkbox"/> Discharge Summary   |
| <input checked="" type="checkbox"/> Consultation Reports   | <input checked="" type="checkbox"/> Operative Reports   | <input checked="" type="checkbox"/> Hospital Chart (Entire)   |
| <input type="checkbox"/> History and Physical Exam   | <input checked="" type="checkbox"/> Pathology Reports   | <input checked="" type="checkbox"/> Autopsy/Toxicology Report/Photos  |
| <input type="checkbox"/> Progress Notes/Orders   | <input checked="" type="checkbox"/> Diagnostic Studies  | <input checked="" type="checkbox"/> Funeral Related Records   |
| <input type="checkbox"/> Lab and Test Reports/Results  | <input checked="" type="checkbox"/> Office Notes/Visits   | <input type="checkbox"/> Psychological/Psychiatric Records  |
| <input type="checkbox"/> Radiology Reports/Studies   | <input checked="" type="checkbox"/> Medication/Prescription   | <input checked="" type="checkbox"/> Billing Records/Itemized Statements   |
| <input type="checkbox"/> Radiology/Studies films/Images  | <input checked="" type="checkbox"/> Emergency Trans   | <input checked="" type="checkbox"/> Hospital Billing Records  |
| <input checked="" type="checkbox"/> Emergency Medical Transport & Health Record (Assessment & Treatment) | <input checked="" type="checkbox"/> Rehabilitation: Physical/Speech/Occupational/Recreational Records | <input checked="" type="checkbox"/> Records from all other providers: Clinic, Office, Chiropractor, Acupuncturist, Therapist, Counselor, Care Providers, etc. |

Other (specify): OB/GYN and related procedures, examination, testing, treatment and/or medical care surrounding any pregnancies for patient, included or excluded in above-defined medical and health records.

**LIEN RECORDS:**

Detailed Health Care Lien/Subrogation/Claims History Information

**DRUG and/or ALCOHOL ABUSE and/or PSYCHIATRIC, and/or HIV/AIDS RECORDS RELEASE:**

\_\_\_\_ I authorize Custodian of Records to release my medical billing records containing information in reference to Drug and/or Alcohol Abuse and Treatment including any substance abuse, Behavioral or Mental Health/Psychiatric Treatment/Testing, and/or HIV/AIDS (Acquired Immunodeficiency Syndrome) Testing/Treatment information or Sexually Transmitted Disease Information) or \_\_\_\_ I authorize release of the records described above, with the following exception(s): \_\_\_\_\_

**PURPOSE OF DISCLOSURE/USE:** Civil Litigation

**TO WHO AND WHERE TO SEND DISCLOSED HEALTH INFORMATION:**

I authorize the disclosure and use of the Health Information described above to the following person(s) or organization(s):

**Lieff Cabraser Heimann & Bernstein**  
275 Battery Street, 29<sup>th</sup> Floor  
San Francisco, CA 94111  
Phone: 415-956-1000  
Fax: 415-956-1008

**RE-DISCLOSURE:**

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Signature of Patient/Authorized Representative (include relationship or nature of authority)

NAME: \_\_\_\_\_ DATE: \_\_\_\_\_

**IF UNDER 18 YEARS OF AGE, PARENT/GUARDIAN SIGNATURE REQUIRED:  
(BOTH PARENTS REQUESTED):**

MOTHER:	(b)(6)	SSN#:	(b)(6)
FATHER:		SSN#:	
GUARDIAN:	_____ SSN#: _____		

**From:** [Finer, Neil](#)  
**To:** [Gantz, Marie](#); [WCarlo@peds.uab.edu](#); [Rich, Wade](#); [ROGER.FAIX@HSC.UTAH.EDU](#); [Bradley.Yoder@hsc.utah.edu](#); [Michele.Walsh@UHhospitals.org](#); [nxs5@case.edu](#); [ALaptook@WIHRI.org](#); [Kurt.Schibler@cchmc.org](#); [Das, Abhik](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: SUPPORT ROP/SpO2 secondary paper  
**Date:** Wednesday, July 24, 2013 12:47:00 PM  
**Attachments:** [ROP secondary 2013-07-11 MW and NE rev July 24 .docx](#)

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Hi Marie

Sorry to be so long with this

I added comments and corrections to Michele's draft

Some comments are in the actual manuscript with only 1 comment#14 added

Overall

This for me is a very sophisticated statistical exercise which will be over the top for most reviewers

There needs to be a better explanation of some of the techniques

I do not see the added value of the figures and Figure 2 is incomprehensible to me

In the discussion you mention "Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).<sup>3</sup>"

This I think needs expansion or should not be included

Nothing in your current paper distinguished the hi from low SpO2 groups by results

I hope these comments and suggestions are helpful

Neil

From: <Gantz>, Marie Gantz <[mgantz@rti.org](mailto:mgantz@rti.org)<<mailto:mgantz@rti.org>>>

Date: Thursday, July 11, 2013 2:25 PM

To: [Wally Carlo](#) <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)<<mailto:wcarlo@peds.uab.edu>>>, [Neil Finer](#) <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)<<mailto:nfiner@ucsd.edu>>>, [Wade Rich](#) <[wrich@ucsd.edu](mailto:wrich@ucsd.edu)<<mailto:wrich@ucsd.edu>>>, [Roger Faix](#) <[Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)<<mailto:Roger.Faix@hsc.utah.edu>>>, "[Bradley.yoder@hsc.utah.edu](#)<<mailto:Bradley.yoder@hsc.utah.edu>>" <[Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)<<mailto:Bradley.yoder@hsc.utah.edu>>>, [Michele Walsh](#) <[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)<<mailto:Michele.Walsh@UHhospitals.org>>>, [nancy newman](#) <[nxs5@case.edu](mailto:nxs5@case.edu)<<mailto:nxs5@case.edu>>>, [Abbot Laptook](#) <[ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org)<<mailto:ALaptook@WIHRI.org>>>, "[kurt.schibler@cchmc.org](#)<<mailto:kurt.schibler@cchmc.org>>" <[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)<<mailto:kurt.schibler@cchmc.org>>>, [Abhik Das](#) <[adas@rti.org](mailto:adas@rti.org)<<mailto:adas@rti.org>>>, [Rosemary Higgins](#) <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>>

Subject: SUPPORT ROP/SpO2 secondary paper

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

Marie Gantz, Ph.D.

Senior Research Statistician

RTI International

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919-597-5110

ROP Secondary  
(07/11/2013)

Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

**Comment [mw1]:** Suggest that title should say Baseline Oxygen Saturation or Actual Oxygen Saturations which will distinguish it from the secondary on intermittent hypoxia the Julie DiFiore and I are working on.

Marie G. Gantz, Ph.D.<sup>1</sup>; Waldemar A. Carlo, M.D.<sup>2</sup>; Neil N. Finer, M.D.<sup>3</sup>; Wade Rich, RRT<sup>3</sup>; Roger G. Faix, M.D.<sup>4</sup>; Bradley Yoder, M.D.<sup>4</sup>; Michele C. Walsh, M.D., M.S.<sup>5</sup>; Nancy Newman, R.N.<sup>5</sup>; Abbot Laptook, M.D.<sup>6</sup>; Kurt Schibler, M.D.<sup>7</sup>; Abhik Das, Ph.D.<sup>8</sup>; Rosemary D. Higgins, M.D.<sup>9</sup>; for the SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

<sup>1</sup>RTI International, Research Triangle Park, North Carolina; <sup>2</sup>University of Alabama at Birmingham, Birmingham, Alabama; <sup>3</sup>University of California, San Diego, San Diego, California; <sup>4</sup>University of Utah, Salt Lake City, Utah; <sup>5</sup>Case Western Reserve University, Cleveland, Ohio; <sup>6</sup>Women and Infants Hospital of Rhode Island, Providence, Rhode Island; <sup>7</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; <sup>8</sup>RTI, Rockville, Maryland; <sup>9</sup>Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Short title: Oxygen saturations and retinopathy of prematurity

Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute

ROP Secondary  
(07/11/2013)

**Word count**

Abstract: 145

Text: 2,786

**Abbreviations:**

AOR = Adjusted odds ratio

CI = Confidence interval

GA = Gestational age

IVH = Intraventricular hemorrhage

NEC = Necrotizing enterocolitis

PMA = Postmenstrual age

PVL = Periventricular leukomalacia

ROP = Retinopathy of prematurity

SGA = Small for gestational age

SpO<sub>2</sub> = Oxygen saturation

ROP Secondary  
(07/11/2013)

## ABSTRACT

### Objective

To identify specific oxygen saturation levels associated with severe ROP among infants in the SUPPORT trial.

### Study Design

Data on oxygen saturation and supplementation were collected up to 36 weeks postmenstrual age or to severe ROP determination for 984 surviving infants. Logistic regression models were created to predict severe ROP.

### Result

Percentage of days on supplemental oxygen (adjusted odds ratio(AOR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age (<10<sup>th</sup> percentile), severe illness (fraction of inspired oxygen >0.4 and on ventilator for >8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP.

### Conclusion

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

### Keywords

Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

ROP Secondary  
(07/11/2013)

## Introduction

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to increases with decreasing gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP decreased with exposure to restricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.<sup>1</sup> However, the resultant practice of restricting oxygen supplementation, usually to no more than 50% inspired oxygen concentration, regardless of the degree of hypoxia created, and without the ability to monitor tissue oxygen delivery was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup>

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval (CI) 0.37 – 0.73,  $p < 0.001$ , number needed to treat = 11), and the duration of oxygen supplementation among survivors was shorter.<sup>3</sup> However, a slight significant (I think slight conveys a different message – NF) but unexpected increase in mortality was seen (x% vs Y%) increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.<sup>5</sup> An additional trial did not show any difference in mortality. (COT) I would perhaps mention this in the discussion – but we are working on the meta analyses and these will show an overall increase in mortality for the low SpO2 group NF)

Data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.<sup>6-8</sup> In three pre-post design cohort studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated

**Comment [mw2]:** In SUPPORT and in followup infants with severe ROP were not blind.

**Comment [mw3]:** Given the current controversies--- need to be very careful and clear about the language.

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**Comment [mw4]:** Would say it the other way around: within a narrow range of generally accepted oxygen saturation values it was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end.

**Comment [MG5]:** Wally; Correct?

**Comment [mw6]:** Would delete altogether. Not needed here.

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ROP Secondary  
(07/11/2013)

with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.<sup>7,11,12</sup> Although a multicenter observational study did not report a significant association between partial pressure of oxygen (PaO<sub>2</sub>) levels and retinopathy,<sup>9</sup> a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels  $\geq$  80mmHg.<sup>10</sup> While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets and about the specific oxygen saturation levels that are associated with ROP.

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Thus, ~~we sought to determine there is a need to determine~~ the oxygen saturation levels that were associated with severe ROP among survivors in the SUPPORT trial to assist in the selection of safe oxygen saturation targets that optimize survival but do not increase the risk of severe ROP. In SUPPORT infants were randomized to lower saturation targets (85-89%) versus higher saturation targets (91-95%) but the actual saturation levels achieved differed from those targeted and This is important because the actual oxygen saturation levels achieved differed from the targets in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably. Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities also are associated with a higher risk of severe ROP. This study tests the hypothesis that there are oxygen saturation levels that increase the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that duration of oxygen exposure, demographic characteristics, gestational age, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

#### Subjects and Methods

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This was a secondary analysis of the data from the oxygen saturation SUPPORT trial. As described previously,<sup>3</sup> surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks' postmenstrual age (PMA) and continued until the severe ROP outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group<sup>13,14</sup>) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy.

Respiratory support data, including mode of support and fraction of inspired oxygen, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days of life through 36 weeks' PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life and every 6 hours thereafter through 36 weeks' PMA or death, transfer or discharge.

Oxygen saturation data were sampled every 10 seconds ~~were collected~~ while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks' PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant.

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Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, oxygen saturation ( $SpO_2$ ) values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value). Display, not actual,  $SpO_2$  values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some  $SpO_2$  values there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each  $SpO_2$  value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved. In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead. These 2 sentences need explaining to the reader – most reviewers will not understand – including me!!

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with  $SpO_2$  values of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

The percent of time spent at various  $SpO_2$  values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using chi-square and Wilcoxon rank

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sums tests. Both the total number of days and the percentage of days spent on supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at each SpO<sub>2</sub> value (<70%, 70%, 71%, ..., 100%) while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO<sub>2</sub> value that best discriminated between infants with and without severe ROP. This discriminant function was interpreted by measuring the correlation between it and the original percentages of time at each SpO<sub>2</sub> value.

SpO<sub>2</sub> values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP. Because of previous associations found between ROP and higher oxygen saturations, the percentages of time spent in the SpO<sub>2</sub> ranges of 96-100%, 97-100%, 98-100%, 99-100%, and 100% were also explored as predictors of severe ROP. Additional covariates were the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age (<10<sup>th</sup> percentile)<sup>4</sup> (SGA), any receipt of antenatal steroids, severe illness defined as FiO<sub>2</sub> > 0.4 and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted carbon dioxide (CO<sub>2</sub>) in the first 14 days of life, periventricular leukomalacia (PVL), grade III or ~~intra~~intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late-onset sepsis or meningitis. For PVL, severe IVH, NEC, and late-onset sepsis or meningitis, only morbidities that occurred before the date of severe ROP outcome determination were included.

**Comment [mw7]:** Need to justify this as a measure of severity of illness as it doesn't match anything a neonatologist would see as severe.

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Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined and for the subset of infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. Due to the reduced number of infants available for the second analysis, the logistic regression model was reduced using backward selection, and only predictors that were statistically significant at the  $p < 0.05$  level were retained in the final model.

Comment – this section – methods is very statistically sophisticated and matbe overkill if this manuscript is intended for a clinical journal NE

### Results

Of the 984 SUPPORT infants who survived to discharge and had the severe ROP ophthalmologic outcome determined, 132 (13%) were diagnosed with severe ROP. The median number of days on which supplemental oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54– 74) and 43.5 for infants without severe ROP (IQR 18– 63) (Wilcoxon rank sums test  $p < 0.001$ ). Ninety-five percent (125/132) of infants with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks' PMA or severe ROP- ophthalmologic outcome determination compared to 64% (541/852) of infants without severe ROP (chi-square  $p < 0.001$ ). Forty-five percent (60/132) of infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of infants without severe ROP (chi-square  $p < 0.001$ ). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP and 0.94 among those without severe ROP).

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had a ophthalmologic ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP. The distributions were similar for the two groups, particularly with respect to the

**Comment [mw8]:** I understand what you mean but it will not make sense to readers outside of the trial.

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**Comment [mw9]:** not sure this helps me. Why included?

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**Comment [WC10]:** Is there a statistical test that we should do to prove that they are similar?

MG: I am working on whether I can do a statistical test comparing these distributions.

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median percent of time spent at each SpO<sub>2</sub> value. In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO<sub>2</sub> values less than 80% (correlations between the discriminant function and percentages of time at SpO<sub>2</sub> values <80% were all >0.5) (Figure 2). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks' PMA or severe ROP ophthalmologic outcome determination and randomized treatment group?? was predictive of severe ROP (adjusted odds ratio (AOR) for a 5% increase in percent of days on supplemental oxygen: 1.14, 95% CI 1.06– 1.22, p<0.001), but percent of time while on supplemental oxygen with SpO<sub>2</sub><80% was not (AOR for a 5% increase in percent of time with SpO<sub>2</sub>< 80%:1.03, 95% CI 0.68– 1.56, p=0.89). Other significant predictors in the model were severe illness, late-onset sepsis or meningitis, GA, SGA, and clinical center (Table). When the percentages of time spent in SpO<sub>2</sub> ranges between 96% and 100% were investigated as predictors of severe ROP, none were statistically significant. When number of days was substituted for percent of days receiving supplemental oxygen, it did not reach significance as a predictor of severe ROP (AOR 1.02, 95% CI 0.999– 1.03, p=0.06); otherwise model results were similar.

Figure 3 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination. The distributions were similar for infants with and without severe ROP, although infants with severe ROP spent a slightly higher percent of time with saturations near 100%. In multivariate analysis of this subset of infants, severe ROP was most highly associated with a greater percentage of time with an SpO<sub>2</sub> of 100% (correlation of 0.35 between discriminant function and percentage of time with SpO<sub>2</sub>=100%) (Figure 2). This variable was also significant in the logistic regression model to predict severe ROP (AOR for a 5% increase in percent of time with an SpO<sub>2</sub> of 100%:2.71, 95% CI 1.05– 6.96,

**Comment [mw11]:** I am having great deal of difficulty understanding this. Needs more explanation and a very thorough legend. Severe ROP was highly assoc with Sar less than 80%???  
If this is stated correctly, need to discuss more thoroughly- why might this be???

**Comment [WC12]:** Statistical test needed to prove similarity?

MG: I am working on whether I can do a statistical test comparing these distributions.

**Comment [WC13]:** Significant? Do we need "slightly"?

MG: I am working on whether I can do a statistical test comparing these distributions.

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p=0.04). Other significant predictors were severe illness, late-onset sepsis or meningitis, male gender, GA, and SGA (Table). When the percentage of time with an SpO<sub>2</sub> of 100% was replaced in the model by percentages of time spent in other SpO<sub>2</sub> ranges between 96% and 100%, the ranges of 99-100% and 96-100% were statistically significant (AOR for a 5% increase in percent of time with SpO<sub>2</sub>99-100%: 1.68, 95% CI 1.02 – 2.77, p = 0.04; AOR for a 5% increase in percent of time with SpO<sub>2</sub>96-100%: 1.27, 95% CI 1.04 – 1.55, p = 0.02) (Figure 4) while estimates for other predictors in the model remained similar. Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup of infants.

**Comment [NF14]:** I think this section about Spo2 of 100 or 96-100 is a bit overdone

**Comment [WC15]:** How about other ranges (e.g. 97-100%, 96-99%, etc)? It is very important if these are NS.

MG: I want to avoid adding too many overlapping tests. What we have done so far is consistent with the analysis that was presented at PAS.

#### Discussion

Infants enrolled in SUPPORT who survived to discharge and were diagnosed with severe ROP spent significantly more time on supplemental oxygen on the days leading up to before 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to survivors without severe ROP. Logistic regression modeling showed that more time on oxygen was a significant risk factor for severe ROP after adjusting for baseline covariates. For infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination, a greater percentage of time with an oxygen saturation of 100% was a significant risk factor for severe ROP. The percentages of time spent in SpO<sub>2</sub> ranges of 99-100% and 96-100% were also statistically significant predictors, but the odds ratios decreased as the ranges expanded away from 100%. These results support the idea that the primary modifiable risk factors for severe ROP may be limited to avoiding extremely high oxygen saturations and reducing the amount of time spent on supplemental oxygen. Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).<sup>3</sup> I agree that this needs to be better detailed here and perhaps with some actual data

**Comment [mw16]:** What happened to the finding of sats < 80%...??

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ROP Secondary  
(07/11/2013)

*[Need to add more interpretation of results.]*

A limitation of the study is that some oximeter data needed to be interpolated due to the lack of a one-to-one match between the skewed SpO<sub>2</sub> values displayed by the oximeters and actual saturations. However, this did not affect SpO<sub>2</sub> values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the SUPPORT oximeter data, the most likely impact of including time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

Other trials designed to target oxygen saturations similarly to SUPPORT have been completed<sup>5</sup> and could perform similar analyses. Previous large studies of associations of oxygen saturation levels and ROP reported targeted but not achieved saturations.<sup>7-9</sup>

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks'PMA is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower\_GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks'PMA or severe ROP outcome determination, less time spent on oxygen with anSpO<sub>2</sub> of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

**Comment [WC17]:** I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

ROP Secondary  
(07/11/2013)

**Acknowledgements**

These should be brief, and should include sources of support including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially.

**Conflict of Interest**

Authors must declare whether or not there is any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper. Conflict of interest should also be noted on the cover letter and as part of the submission process. See the Conflict of Interest documentation in the Editorial Policy section for detailed information.

ROP Secondary  
(07/11/2013)

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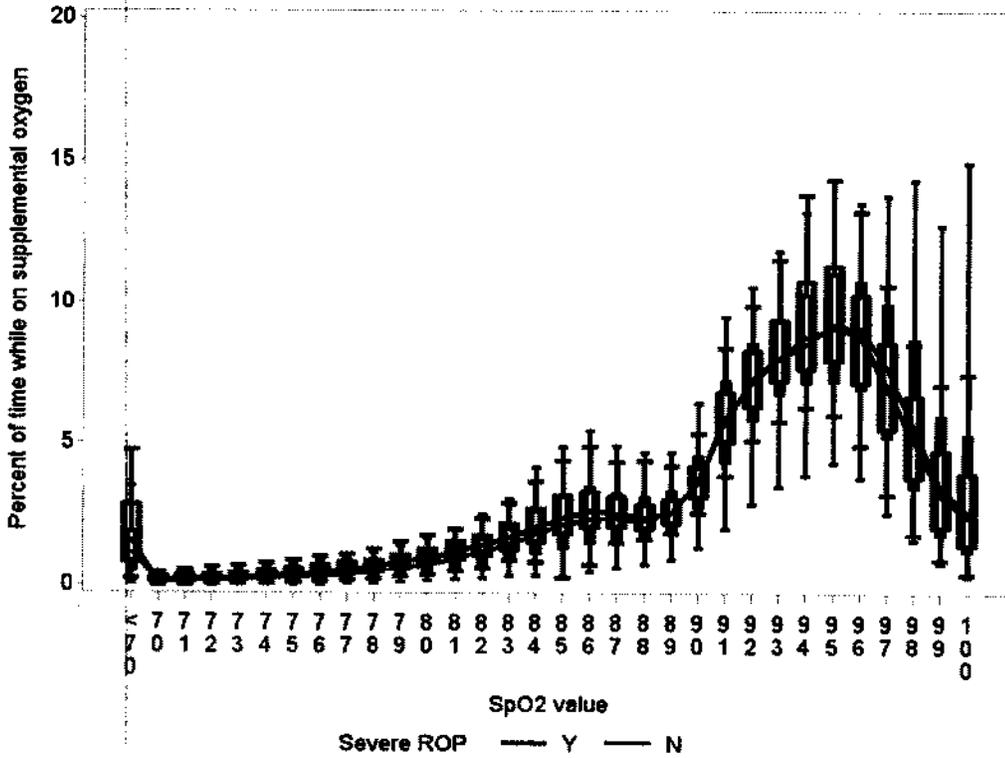
ROP Secondary  
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ROP Secondary  
(07/11/2013)

Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination (N=932)

**Comment [WC18]:** I prefer to include interpretation of the results in figures legends also. Most journals use that style.

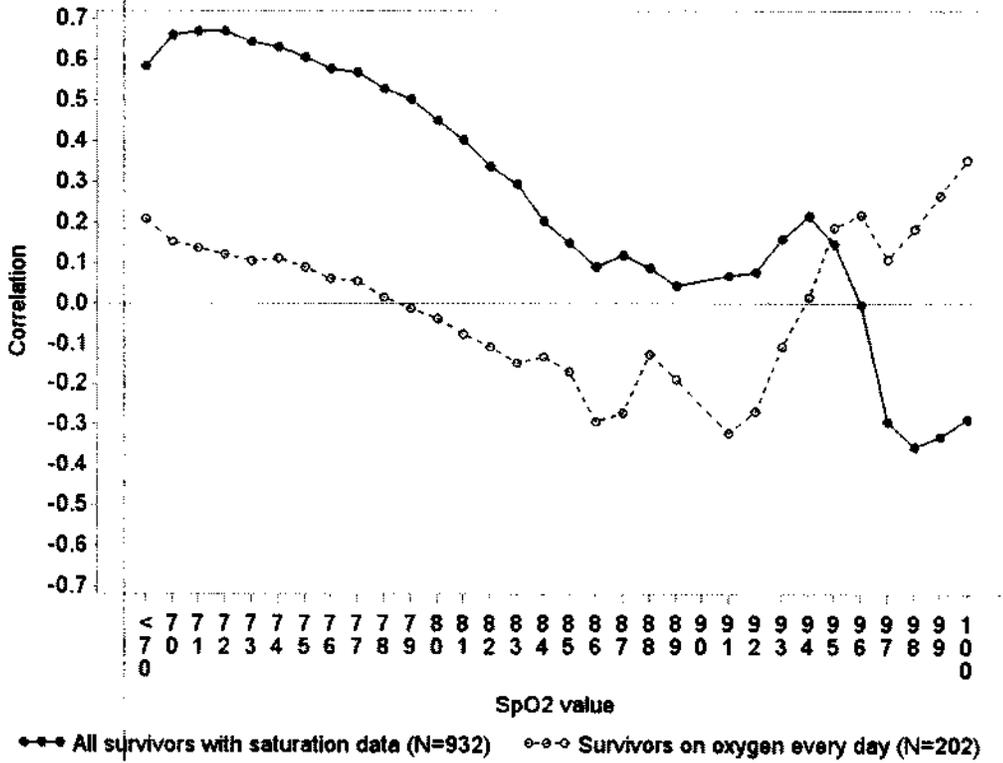


Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

ROP Secondary  
(07/11/2013)

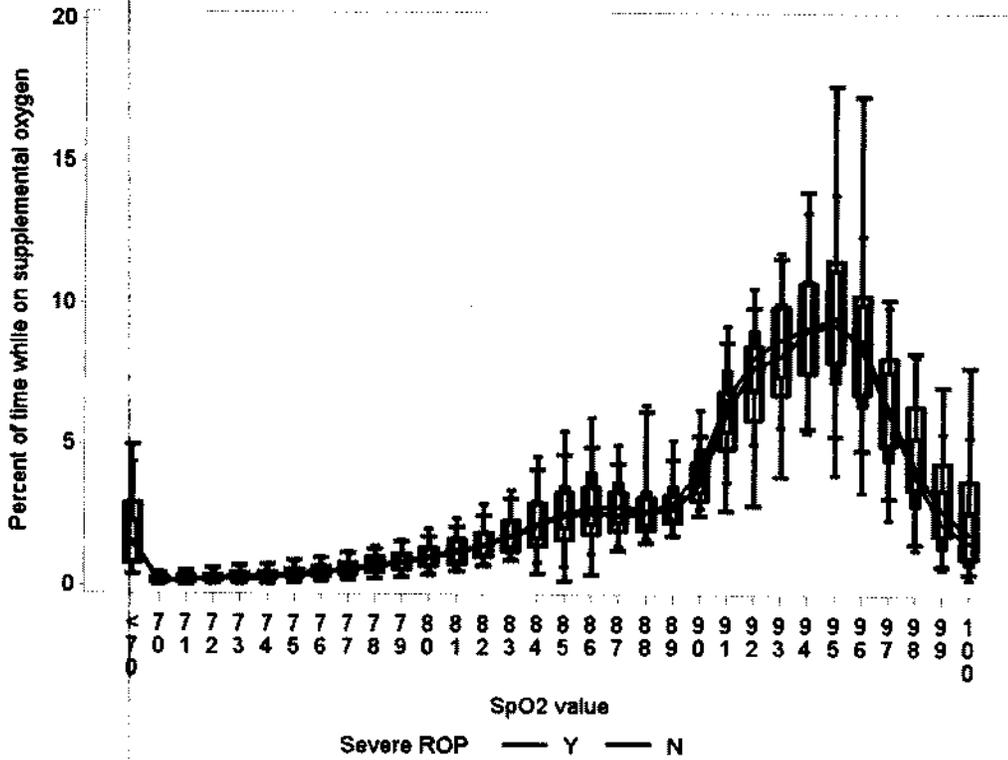
Figure 2. Correlation between discriminant functions from multivariate analyses and percentage of time spent at each SpO2 value while on supplemental oxygen: a measure of association between percentage of time spent at each SpO2 value and severe ROP

**Comment [MG19]:** I would be alright with getting rid of this figure if it seems confusing.



ROP Secondary  
(07/11/2013)

Figure 3. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP - ophthalmologic outcome determination for infants who received oxygen each day (N=202)



Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

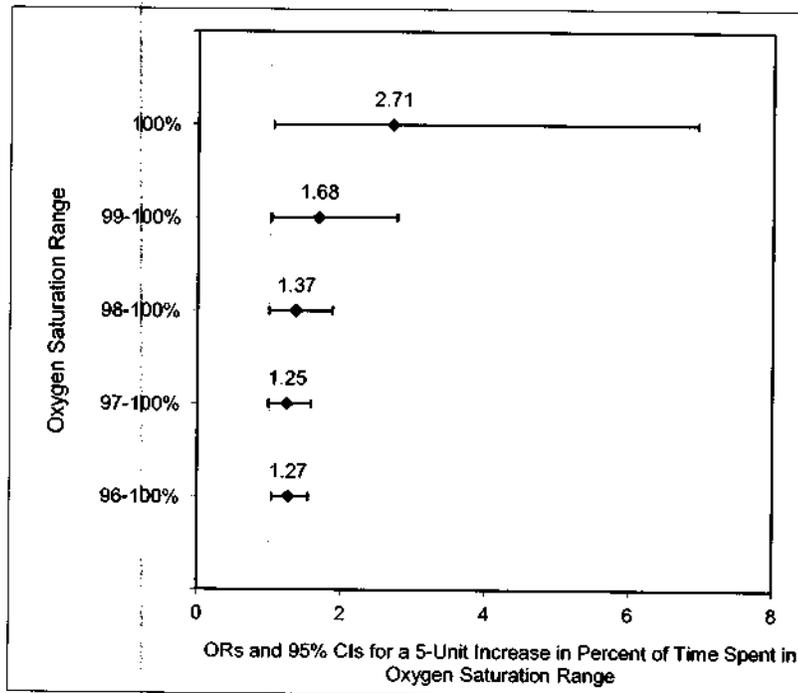
ROP Secondary  
(07/11/2013)

Table. Models predicting severe ROP among survivors to discharge

	Model for all survivors to discharge			Model for survivors who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome		
	Adjusted OR	Adjusted 95% CI	P value	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06 – 1.22)	<0.001			
Percent of time with SpO2<80% (unit=5% increase)	1.03	(0.68 – 1.56)	0.89			
Percent of time with SpO2=100% (unit=5% increase)				2.71	(1.05 – 6.96)	0.04
Severe illness	3.50	(2.05 – 5.97)	<0.001	2.48	(1.04 – 5.90)	0.04
Time weighted CO <sub>2</sub> in the first 14 days of life	0.99	(0.95 – 1.03)	0.60			
PVL	2.09	(0.83 – 5.28)	0.12			
IVH grade 3-4	1.10	(0.53 – 2.28)	0.79			
NEC	1.11	(0.53 – 2.30)	0.78			
Late-onset sepsis or meningitis	2.11	(1.31 – 3.39)	0.002	2.31	(1.13 – 4.72)	0.02
Any antenatal steroids	0.49	(0.13 – 1.92)	0.31			
Male	1.23	(0.77 – 1.96)	0.38	2.38	(1.13 – 5.00)	0.02
Gestational age (weeks)	0.49	(0.38 – 0.63)	<0.001	0.45	(0.30 – 0.68)	<0.001
Small for gestational age	2.38	(1.04 – 5.47)	0.04	4.06	(1.35 – 12.23)	0.01
Race/ethnicity (vs. Non-Hispanic White)			0.21			
Non-Hispanic Black	0.54	(0.30 – 0.99)				
Hispanic	0.89	(0.43 – 1.84)				
Other	1.16	(0.35 – 3.82)				
Center			0.15			

ROP Secondary  
(07/11/2013)

Figure 4. The effect of time spent in various oxygen saturation ranges in models predicting severe ROP among survivors to discharge who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome



**From:** Walsh, Michele  
**To:** Kristi Watterberg (kwatterberg@salud.unm.edu); rose higgins  
**Subject:** NRN steering committee  
**Date:** Wednesday, July 24, 2013 11:50:01 AM

---

Hi: I am just getting back from (b)(6)  
(b)(6) will be flying in tomorrow  
And therefore will miss the HC subcommittee meeting-  
Sorry Kristi!

*Michele Walsh*  
**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo (wacarlo@uab.edu)  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Wednesday, July 24, 2013 9:49:47 AM

---

RE severity criteria: boy I must have missed that subcommittee call when these severity criteria were selected!  
Still need to defend them in some way both in this and in the growth paper.  
By what criteria were these chosen, because many will not believe that FiO2 > 0.4 and MV for >8hrs in first 15 days is severe.  
Should saturation analysis by quartiles be included in this paper rather than in growth?

*Michele Walsh*  
**Chief Division of Neonatology**  
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**Professor of Pediatrics**  
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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, July 24, 2013 8:51 AM  
**To:** 'Wally Carlo, M.D.'; Walsh, Michele; Gantz, Marie; nfiner@ucsd.edu; wrich@ucsd.edu; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

I added my comments with Wally's and Michele's  
Rose

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**To:** Walsh, Michele; Gantz, Marie; nfiner@ucsd.edu; wrich@ucsd.edu; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das,

Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

I have added my comments to those of Michele. I think Michele raises very important points.

Wally

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Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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**From:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Tuesday, July 23, 2013 3:29 PM  
**To:** Gantz, Marie; Wally Carlo, M.D.; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); [nxs5@case.edu](mailto:nxs5@case.edu); [ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); Das, Abhik; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

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I have embedded comments in track change.

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In first 15 days. How was this determined? It will raise eyebrows. I suspect it was determined by some statistical cutpoint??
3. I do not understand Figure 2 and interpretation at all.  
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This is not mentioned in the discussion and I do not understand what it means... seems to contradict the results of the main trial.
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**From:** Gantz, Marie [<mailto:mgantz@rti.org>]

**Sent:** Thursday, July 11, 2013 2:26 PM

**To:** [WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); Walsh, Michele; [nxs5@case.edu](mailto:nxs5@case.edu); [ALaptook@WIHRI.org](mailto:ALaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); Das, Abhik; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**Subject:** SUPPORT ROP/SpO2 secondary paper

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

Marie Gantz, Ph.D.

Senior Research Statistician

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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Guttmacher, Alan (NIH/NICHD) [E]  
**Sent:** Wednesday, July 24, 2013 9:33 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]  
**Cc:** Jarman, John (NIH/NICHD) [E]  
**Subject:** RE: OIG inquiry

Sounds good. Just give them the facts.

Alan

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, July 24, 2013 9:33 AM  
**To:** Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]  
**Cc:** Jarman, John (NIH/NICHD) [E]  
**Subject:** FW: OIG inquiry

Hi

I spoke to Valerie Bonham yesterday.

The meeting with the OIG is being set up for next week – Tiffany Brown from OMA will attend and Dr. Stephanie Devaney is also likely to attend.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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---

**From:** Brown, Tiffany (NIH/OD) [E]  
**Sent:** Tuesday, July 23, 2013 3:16 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: OIG inquiry

Hi Dr. Higgins,

The OIG is not available on tomorrow. Are you still available on Monday, July 29<sup>th</sup> at 1pm?

**TIFFANY BROWN**

NIH/OD/OMA

(301) 496-2464 - DIRECT

(301) 402-0169 - FAX

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

**Sent:** Tuesday, July 23, 2013 12:53 PM

**To:** Galvin, Chris P (OIG/OEI)

**Cc:** Brown, Tiffany (NIH/OD) [E]

**Subject:** RE: OIG inquiry

Hi

I believe Tiffany Brown is working on the meeting date and time. She should be in contact with you regarding the date/time.

Regards

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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**From:** Galvin, Chris P (OIG/OEI)

**Sent:** Tuesday, July 23, 2013 11:04 AM

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

**Subject:** OIG inquiry

Dr. Higgins,

I apologize for reaching out to you directly, but I haven't heard from either of our respective liaisons. When we were given your availability for this week, we requested 1:00 PM slot today. We have not heard whether this a confirmed meeting or not. Please advise.

Thank you.

Chris Galvin

DHHS/OIG/OEI

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Miami Lakes, FL 33016

Direct phone (305) 536-7211

Fax (305) 530-7759

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Walsh, Michele"; "Gantz, Marie"; "nfiner@ucsd.edu"; "wrich@ucsd.edu"; "ROGER.FAIX@HSC.UTAH.EDU"; "Bradley.Yoder@hsc.utah.edu"; "nxs5@case.edu"; "ALaptook@WIHRI.org"; "Kurt.Schibler@cchmc.org"; "Das, Abhik"  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Wednesday, July 24, 2013 8:50:34 AM  
**Attachments:** ROP secondary 2013-07-11 with notes mw commentswc.docx

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(07/11/2013)

Achieved Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

**Comment [mw1]:** Suggest that title should say Baseline Oxygen Saturation or Actual Oxygen Saturations which will distinguish it from the secondary on intermittent hypoxia the Julie DiFiore and I are working on.

**Comment [WC2]:** I agree. Achieved is the word Hagadom used in the best study that was designed to compare targets vs actual stas.

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Short title: Oxygen saturations and retinopathy of prematurity

Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute

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Word count

Abstract: 145

Text: 2,786

Abbreviations:

AOR = Adjusted odds ratio

CI = Confidence interval

GA = Gestational age

IVH = Intraventricular hemorrhage

NEC = Necrotizing enterocolitis

PMA = Postmenstrual age

PVL = Periventricular leukomalacia

ROP = Retinopathy of prematurity

SGA = Small for gestational age

SpO<sub>2</sub> = Oxygen saturation

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## ABSTRACT

### Objective

To identify specific oxygen saturation levels associated with severe ROP among infants in the SUPPORT trial.

### Study Design

Data on oxygen saturation and supplementation were collected up to 36 weeks postmenstrual age or to severe ROP determination for 984 surviving infants. Logistic regression models were created to predict severe ROP.

### Result

Percentage of days on supplemental oxygen (adjusted odds ratio (AOR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age (<10<sup>th</sup> percentile), severe illness (fraction of inspired oxygen > 0.4 and on ventilator for > 8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP.

### Conclusion

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

### Keywords

Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

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## Introduction

Retinopathy of prematurity (ROP) is an ~~important~~ cause of ~~blindness and other~~ visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP decreased with exposure to restricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.<sup>1</sup> However, the resultant practice of uncontrolled restriction of oxygen supplementation, usually to no more than 50% inspired oxygen concentration, regardless of the degree of hypoxia created, and without the ability to monitor oxygenation continuously/tissue oxygen delivery was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup>

**Comment [mw3]:** In SUPPORT and in followup infants with severe ROP were not blind.

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval (CI) 0.37 – 0.73,  $p < 0.001$ , number needed to treat = 11), and the duration of oxygen supplementation among survivors was shorter.<sup>3</sup> However, a slight but unexpected increase in mortality was seen (16.2% vs 19.9%) increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.<sup>5</sup> An additional trial did not show any difference in mortality. (COT)

**Comment [mw4]:** Given the current controversies-- need to be very careful and clear about the language.

**Comment [rdh5]:** WE need to be clear that these data and conclusions preceded ventilator care, oxygen monitoring and NICU's for VLBW infants

Data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.<sup>6-8</sup> In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.<sup>7,11,12</sup> Although a

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**Comment [mw6]:** Would say it the other way around: within a narrow range of generally accepted oxygen saturation values it was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end.

**Comment [MG7]:** Wally. Correct?

**Comment [mw8]:** Would delete altogether. Not needed here.

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multicenter observational study did not report a significant association between partial pressure of oxygen (PaO<sub>2</sub>) levels and retinopathy,<sup>9</sup> a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels  $\geq 80$  mmHg.<sup>10</sup> While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets and about the specific oxygen saturation levels that are associated with ROP.

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Thus, ~~we sought to determine there is a need to determine~~ the oxygen saturation levels ~~that were associated with severe ROP among survivors in the SUPPORT trial to assist in the selection of safe oxygen saturation targets that optimize survival but do not increase the risk of severe ROP. It was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end within a narrow range of generally accepted oxygen saturation values. In SUPPORT, infants were randomized to lower saturation targets (85-89%) versus higher saturation targets (91-95%) but as expected, the actual saturation levels achieved differed from those targeted and This is important because the actual oxygen saturation levels achieved differed from the targets in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably. Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities also~~ are associated with a higher risk of severe ROP. This study tests the hypothesis that there are oxygen saturation levels that increase the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that duration of oxygen exposure, demographic characteristics, gestational age, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

Comment [WC9]: Quote J Hagadorn study here

Comment [rdh10]: We should also state that target are difficult to maintain in the most critically ill infants due to their labile clinical status.

#### Subjects and Methods

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This was a secondary analysis of the data from the oxygen saturation SUPPORT trial. As described previously,<sup>3</sup> surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks' postmenstrual age (PMA) and continued until the severe ROP outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group<sup>13,14</sup>) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, ~~both laser therapy and cryotherapy~~, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy.

Respiratory support data, including mode of support and fraction of inspired oxygen, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days of life through 36 weeks' PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life and every 6 hours thereafter through 36 weeks' PMA or death, transfer or discharge.

Oxygen saturation data were sampled every 10 seconds ~~were collected~~ while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks' PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant.

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Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, oxygen saturation ( $SpO_2$ ) values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value). Display, not actual,  $SpO_2$  values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some  $SpO_2$  values there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each  $SpO_2$  value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved. In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead.

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with  $SpO_2$  values of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

The percent of time spent at various  $SpO_2$  values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using chi-square and Wilcoxon rank sums tests. Both the total number of days and the percentage of days spent on supplemental oxygen up

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to 36 weeks' PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at each SpO<sub>2</sub> value (<70%, 70%, 71%, ..., 100%) while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO<sub>2</sub> value that best discriminated between infants with and without severe ROP. This discriminant function was interpreted by measuring the correlation between it and the original percentages of time at each SpO<sub>2</sub> value.

SpO<sub>2</sub> values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP. Because of previous associations found between ROP and higher oxygen saturations, the percentages of time spent in the SpO<sub>2</sub> ranges of 96-100%, 97-100%, 98-100%, 99-100%, and 100% were also explored as predictors of severe ROP. Additional covariates were the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age (<10<sup>th</sup> percentile)<sup>4</sup> (SGA), any receipt of antenatal steroids, severe illness defined in SUPPORT as FiO<sub>2</sub> > 0.4 and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted carbon dioxide (CO<sub>2</sub>) in the first 14 days of life, periventricular leukomalacia (PVL), grade III or IV intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late-onset sepsis or meningitis. For PVL, severe IVH, NEC, and late-onset sepsis or meningitis, only morbidities that occurred before the date of severe ROP outcome determination were included.

**Comment [mw11]:** Need to justify this as a measure of severity of illness as it doesn't match anything a neonatologist would see as severe.

**Comment [WC12]:** This was pre-specified by the SUPPORT subcommittee.

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Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined and for the subset of infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. Due to the reduced number of infants available for the second analysis, the logistic regression model was reduced using backward selection, and only predictors that were statistically significant at the  $p < 0.05$  level were retained in the final model.

### Results

Of the 984 SUPPORT infants who survived to discharge and had the severe ROP ophthalmologic outcome determined, 132 (13%) were diagnosed with severe ROP. The median number of days on which supplemental oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54–74) and 43.5 for infants without severe ROP (IQR 18–63) (Wilcoxon rank sums test  $p < 0.001$ ). Ninety-five percent (125/132) of infants with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to 64% (541/852) of infants without severe ROP (chi-square  $p < 0.001$ ). Forty-five percent (60/132) of infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of infants without severe ROP (chi-square  $p < 0.001$ ). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP and 0.94 among those without severe ROP).

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had an ophthalmologic ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP. The distributions were similar for the two groups, particularly with respect to the median percent of time spent at each SpO<sub>2</sub> value. In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO<sub>2</sub> values less than 80%

Comment [mw13]: I understand what you mean but it will not make sense to readers outside of the trial.

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Comment [mw14]: not sure this helps me. Why included?

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Comment [WC15]: Is there a statistical test that we should do to prove that they are similar?

MG: I am working on whether I can do a statistical test comparing these distributions.

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(correlations between the discriminant function and percentages of time at SpO<sub>2</sub> values <80% were all >0.5) (Figure 2). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks' PMA or severe ROP ophthalmologic outcome determination was predictive of severe ROP (adjusted odds ratio (AOR) for a 5% increase in percent of days on supplemental oxygen: 1.14, 95% CI 1.06– 1.22, p<0.001), but percent of time while on supplemental oxygen with SpO<sub>2</sub><80% was not (AOR for a 5% increase in percent of time with SpO<sub>2</sub>< 80%:1.03, 95% CI 0.68– 1.56, p=0.89). Other significant predictors in the model were severe illness, late-onset sepsis or meningitis, GA, SGA, and clinical center (Table). When the percentages of time spent in SpO<sub>2</sub> ranges between 96% and 100% were investigated as predictors of severe ROP, none were statistically significant. When number of days was substituted for percent of days receiving supplemental oxygen, it did not reach significance as a predictor of severe ROP (AOR 1.02, 95% CI 0.999– 1.03, p=0.06); otherwise model results were similar.

**Comment [aw16]:** I am having great deal of difficulty understanding this. Needs more explanation and a very thorough legend. Severe ROP was highly assoc with Sat less than 80%??%??%??  
If this is stated correctly, need to discuss more thoroughly- why might this be???

Figure 3 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination. The distributions were similar for infants with and without severe ROP, although infants with severe ROP spent a slightly higher percent of time with saturations near 100%. In multivariate analysis of this subset of infants, severe ROP was most highly associated with a greater percentage of time with an SpO<sub>2</sub> of 100% (correlation of 0.35 between discriminant function and percentage of time with SpO<sub>2</sub>=100%) (Figure 2). This variable was also significant in the logistic regression model to predict severe ROP (AOR for a 5% increase in percent of time with an SpO<sub>2</sub> of 100%:2.71, 95% CI 1.05– 6.96, p=0.04). Other significant predictors were severe illness, late-onset sepsis or meningitis, male gender, GA, and SGA (Table). When the percentage of time with an SpO<sub>2</sub> of 100% was replaced in the model by

**Comment [WC17]:** Statistical test needed to prove similarity?

MG: I am working on whether I can do a statistical test comparing these distributions.

**Comment [WC18]:** Significant? Do we need "slightly"?

MG: I am working on whether I can do a statistical test comparing these distributions.

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percentages of time spent in other SpO<sub>2</sub> ranges between 96% and 100%, the ranges of 99-100% and 96-100% were statistically significant (AOR for a 5% increase in percent of time with SpO<sub>2</sub> 99-100%: 1.68, 95% CI 1.02 – 2.77, p = 0.04; AOR for a 5% increase in percent of time with SpO<sub>2</sub> 96-100%: 1.27, 95% CI 1.04 – 1.55, p = 0.02) (Figure 4) while estimates for other predictors in the model remained similar. Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup of infants.

**Comment [WC19]:** How about other ranges (e.g. 97-100%, 96-99%, etc)? It is very important if these are NS.

MG: I want to avoid adding too many overlapping tests. What we have done so far is consistent with the analysis that was presented at PAS.

#### Discussion

Infants enrolled in SUPPORT who survived to discharge and were diagnosed with severe ROP spent significantly more time on supplemental oxygen on the days leading up to before 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to survivors without severe ROP. Logistic regression modeling showed that more time on oxygen was a significant risk factor for severe ROP after adjusting for baseline covariates. For infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination, a greater percentage of time with an oxygen saturation of 100% was a significant risk factor for severe ROP. The percentages of time spent in SpO<sub>2</sub> ranges of 99-100% and 96-100% were also statistically significant predictors, but the odds ratios decreased as the ranges expanded away from 100%. These results support the idea that the primary modifiable risk factors for severe ROP may be limited to avoiding extremely high oxygen saturations and reducing the amount of time spent on supplemental oxygen. Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).<sup>3</sup>

**Comment [mw20]:** What happened to the finding of sats < 80%...??

*[Need to add more interpretation of results.]*

A limitation of the study is that some oximeter data needed to be interpolated due to the lack of a one-to-one match between the skewed SpO<sub>2</sub> values displayed by the oximeters and actual saturations.

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However, this did not affect SpO<sub>2</sub> values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the SUPPORT oximeter data, the most likely impact of including time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

Other trials designed to target oxygen saturations similarly to SUPPORT have been completed<sup>5</sup> and could perform similar analyses. Previous large studies of associations of oxygen saturation levels and ROP reported targeted but not achieved saturations.<sup>7-9</sup>

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks' PMA is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower\_GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination, less time spent on oxygen with an SpO<sub>2</sub> of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

**Comment [WC21]:** I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

**Comment [rdh22]:** IS "exposure" a better term?

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**Acknowledgements**

These should be brief, and should include sources of support including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially.

**Conflict of interest**

Authors must declare whether or not there are any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper. Conflict of interest should also be noted on the cover letter and as part of the submission process. See the Conflict of Interest documentation in the Editorial Policy section for detailed information.

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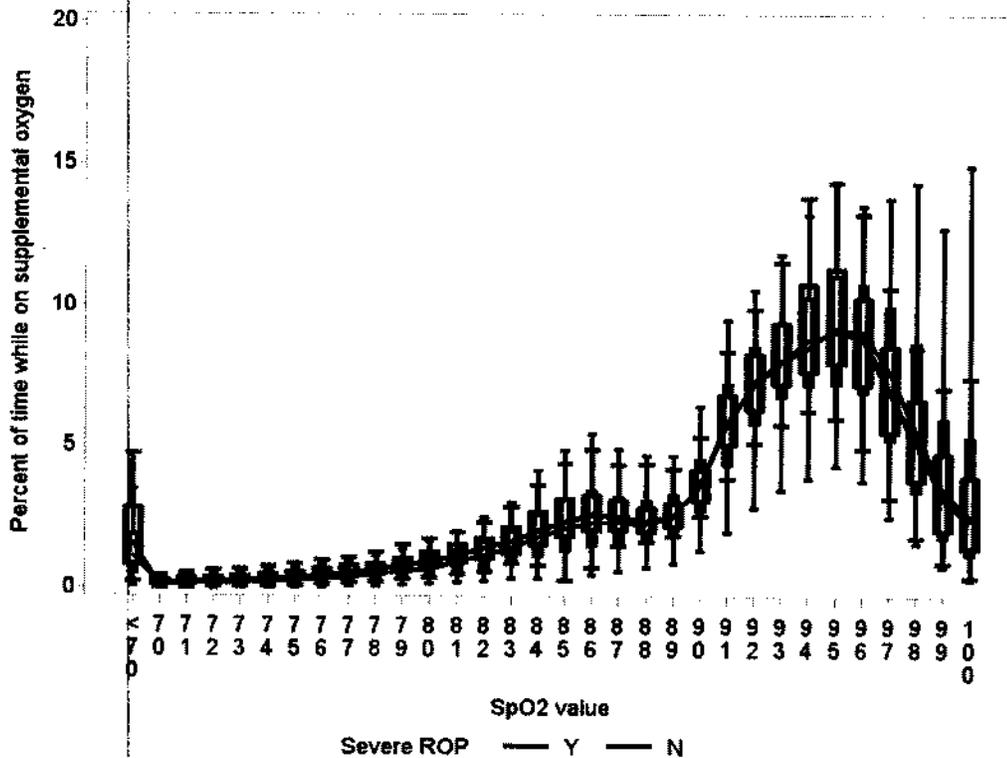
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Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination (N=932)

Comment [WC23]: I prefer to include interpretation of the results in figures legends also. Most journals use that style.

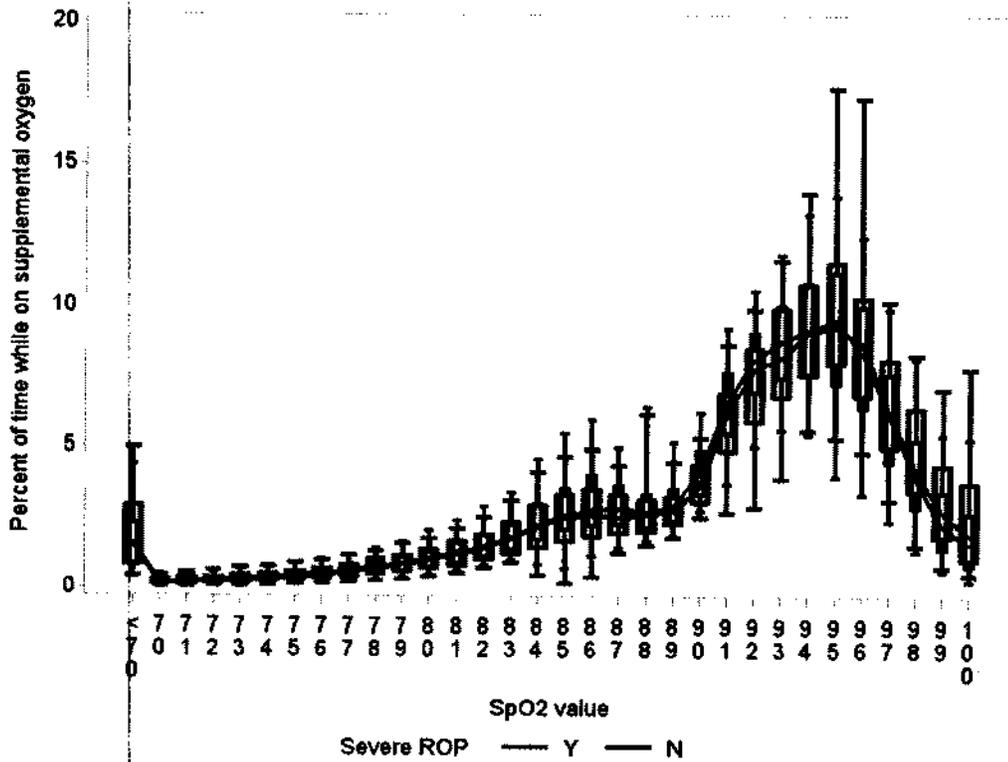


Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.



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Figure 3. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP - ophthalmologic outcome determination for infants who received oxygen each day (N=202)



Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

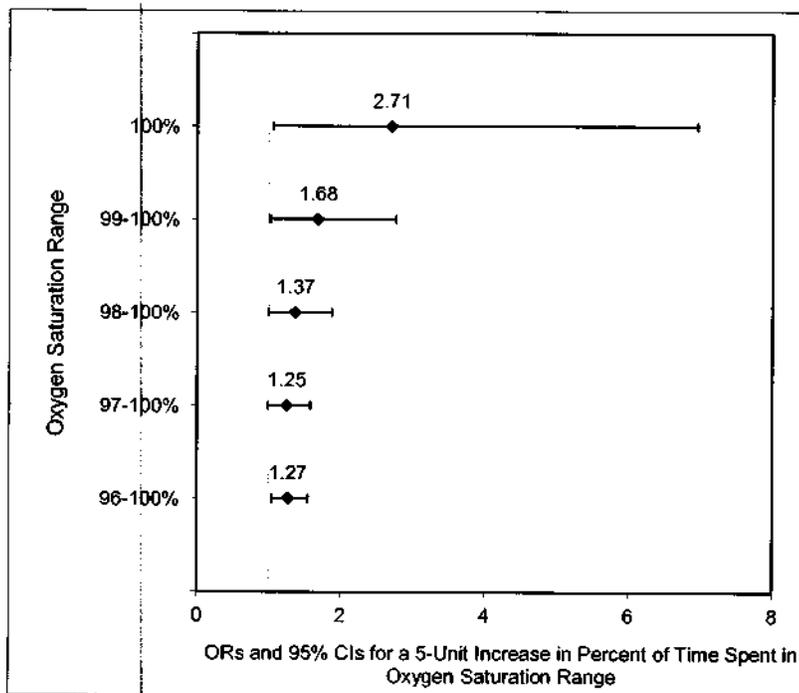
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Table. Models predicting severe ROP among survivors to discharge

	Model for all survivors to discharge			Model for survivors who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome		
	Adjusted OR	Adjusted 95% CI	P value	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06 - 1.22)	<0.001			
Percent of time with SpO2<80% (unit=5% increase)	1.03	(0.68 - 1.56)	0.89			
Percent of time with SpO2=100% (unit=5% increase)				2.71	(1.05 - 6.96)	0.04
Severe illness	3.50	(2.05 - 5.97)	<0.001	2.48	(1.04 - 5.90)	0.04
Time weighted CO <sub>2</sub> in the first 14 days of life	0.99	(0.95 - 1.03)	0.60			
PVI	2.09	(0.83 - 5.28)	0.12			
IVH grade 3-4	1.10	(0.53 - 2.28)	0.79			
NEC	1.11	(0.53 - 2.30)	0.78			
Late-onset sepsis or meningitis	2.11	(1.31 - 3.39)	0.002	2.31	(1.13 - 4.72)	0.02
Any antenatal steroids	0.49	(0.13 - 1.92)	0.31			
Male	1.23	(0.77 - 1.96)	0.38	2.38	(1.13 - 5.00)	0.02
Gestational age (weeks)	0.49	(0.38 - 0.63)	<0.001	0.45	(0.30 - 0.68)	<0.001
Small for gestational age	2.38	(1.04 - 5.47)	0.04	4.06	(1.35 - 12.23)	0.01
Race/ethnicity (vs. Non-Hispanic White)			0.21			
Non-Hispanic Black	0.54	(0.30 - 0.99)				
Hispanic	0.89	(0.43 - 1.84)				
Other	1.16	(0.35 - 3.82)				
Center			0.15			

ROP Secondary  
(07/11/2013)

Figure 4. The effect of time spent in various oxygen saturation ranges in models predicting severe ROP among survivors to discharge who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome



**From:** [Finer, Neil](#)  
**To:** [Das, Abhik](#); [Wally Carlo, M.D.](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: question  
**Date:** Tuesday, July 23, 2013 8:38:16 PM  
**Attachments:** [IMG\\_0001.pdf](#)

---

Hi Abhik  
Here is letter with my signature  
Thanks  
Neil

---

**From:** [Das, Abhik \[mailto:adas@rti.org\]](mailto:adas@rti.org)  
**Sent:** Tuesday, July 23, 2013 1:23 PM  
**To:** [Wally Carlo, M.D.](#); [Finer, Neil](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** FW: question

Wally and Neil:

I have incorporated the few suggestions I got from the Steering Committee. Attached are both the track changes and clean copy versions, which I have also run by the RTI lawyer.

Neil:

Please print, sign, scan and email back to me. I will then add my signature and Wally's to it at the steering committee, and then send off to Dr. Carome.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
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3. As per the data sharing plan proposed by the NRN Data Coordinating Center (DCC) and approved by NIH, if external data sharing is approved by the NRN Steering Committee and NICHD, the DCC will create de-identified limited-access data sets for this purpose. Although the data sets will be stripped of identifiers and otherwise modified to prevent easy identification of patients in the study, the narrow focus of the population to be analyzed and the possible rarity of some outcome measures and risk factors might make it possible for an identification to be made. Therefore, in order to protect the confidentiality and privacy of the subjects, external investigators granted access to these data must adhere to strict requirements defined by the NRN Steering Committee that are incorporated into a standard Data Distribution Agreement to which all external investigators seeking the data must agree to abide and adhere to. The Data Distribution Agreement may be subject to review by the legal departments and IRBs of the DCC and the NRN clinical centers, and must be approved by the Steering Committee. Finally, in accordance with NICHD policies, outside researchers will be required to submit an approval from their IRB for the proposed research.

In summary, in accordance with NIH approved policies, we will not be presently releasing the requested data from the SUPPORT trial. Once the extended follow up for the SUPPORT trial concludes and its primary results are published, the NRN is willing to entertain scientifically rigorous protocols that seek access to the trial data to conduct secondary analyses that may contribute to the science of neonatology. Such requests will need to follow established data sharing policies adopted by the NRN and NIH and adhere to required human subjects protections, as referred to earlier in this letter.

Sincerely

Abhik Das

Waldemar Carlo



Neil Finer

for the NICHD Neonatal Research Network Steering Committee

**From:** [Wally Carlo, M.D.](mailto:Wally.Carlo.M.D.)  
**To:** [Walsh, Michele](mailto:Walsh.Michele); [Gantz, Marie](mailto:Gantz.Marie); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); [nxs5@case.edu](mailto:nxs5@case.edu); [Alaptook@WIHRI.org](mailto:Alaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); [Das, Abhik](mailto:Das.Abhik); [Higgins, Rosemary](mailto:Higgins.Rosemary) (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Wednesday, July 24, 2013 8:28:21 AM  
**Attachments:** [ROP secondary 2013-07-11 with notes mw commentswc.docx](#)

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I have added my comments to those of Michele. I think Michele raises very important points.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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176F Suite 9380R  
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FAX: 205 934 3100  
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**From:** Walsh, Michele [mailto:[Michele.Walsh@UHhospitals.org](mailto:Michele.Walsh@UHhospitals.org)]  
**Sent:** Tuesday, July 23, 2013 3:29 PM  
**To:** Gantz, Marie; Wally Carlo, M.D.; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); [nxs5@case.edu](mailto:nxs5@case.edu); [Alaptook@WIHRI.org](mailto:Alaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); [Das, Abhik](mailto:Das.Abhik); [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper

Overall: given the current environment, I think we need to be extremely careful in the wording of this paper and Of the growth secondary. I have edited language with this cautious lens.

I have embedded comments in track change.

1. Some of the terminology could be altered to improve understanding

For example: timepoint of outcome determination: "36wks PMA or severe ROP determination" Leads to long sentences with the phrase severe ROP three times. Suggest instead "36wks PMA or ophthalmologic determination"

2. Both papers need to provide some justification for the unusual definition of severe illness:  $FiO_2 > 0.4$  and  $> 8$ hrs of mechanical ventilation  
In first 15 days. How was this determined? It will raise eyebrows. I suspect it was determined by some statistical cutpoint??

3. I do not understand Figure 2 and interpretation at all.

Also confused by one section in the results that references figure 2 and states:

"In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with  $SpO_2$  values less than 80% (correlations between the discriminant function and percentages of time at  $SpO_2$  values  $< 80\%$  were all  $> 0.5$ )."

This is not mentioned in the discussion and I do not understand what it means... seems to contradict the results of the main trial.

4. Can the horizontal axis in Figure 1 and Fig 3 be expanded to get the full number horizontally- or maybe just list every other number.

*Michele Walsh*

**Chief Division of Neonatology**  
Rainbow Babies & Childrens Hospital  
**Professor of Pediatrics**  
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email: [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu)  
Phone: (216) 844-3387  
Fax: (216) 844-3380

---

**From:** Gantz, Marie [<mailto:mgantz@rti.org>]  
**Sent:** Thursday, July 11, 2013 2:26 PM  
**To:** [WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [ROGER.FAIX@HSC.UTAH.EDU](mailto:ROGER.FAIX@HSC.UTAH.EDU); [Bradley.Yoder@hsc.utah.edu](mailto:Bradley.Yoder@hsc.utah.edu); Walsh, Michele; [nxs5@case.edu](mailto:nxs5@case.edu); [Alaptook@WIHRI.org](mailto:Alaptook@WIHRI.org); [Kurt.Schibler@cchmc.org](mailto:Kurt.Schibler@cchmc.org); Das, Abhik; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)  
**Subject:** SUPPORT ROP/SpO2 secondary paper

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

Marie Gantz, Ph.D.  
Senior Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
919-547-5110

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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ROP Secondary  
(07/11/2013)

Achieved Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

**Comment [mw1]:** Suggest that title should say Baseline Oxygen Saturation or Actual Oxygen Saturations which will distinguish it from the secondary on intermittent hypoxia the Julie DiFiore and I are working on.

**Comment [WC2]:** I agree. Achieved is the word Hagadorn used in the best study that was designed to compare targets vs actual stas.

Marie G. Gantz, Ph.D.<sup>1</sup>; Waldemar A. Carlo, M.D.<sup>2</sup>; Neil N. Finer, M.D.<sup>3</sup>; Wade Rich, RRT<sup>3</sup>; Roger G. Faix, M.D.<sup>4</sup>; Bradley Yoder, M.D.<sup>4</sup>; Michele C. Walsh, M.D., M.S.<sup>5</sup>; Nancy Newman, R.N.<sup>5</sup>; Abbot Laptook, M.D.<sup>6</sup>; Kurt Schibler, M.D.<sup>7</sup>; Abhik Das, Ph.D.<sup>8</sup>; Rosemary D. Higgins, M.D.<sup>9</sup>; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

<sup>1</sup>RTI International, Research Triangle Park, North Carolina; <sup>2</sup>University of Alabama at Birmingham, Birmingham, Alabama; <sup>3</sup>University of California, San Diego, San Diego, California; <sup>4</sup>University of Utah, Salt Lake City, Utah; <sup>5</sup>Case Western Reserve University, Cleveland, Ohio; <sup>6</sup>Women and Infants Hospital of Rhode Island, Providence, Rhode Island; <sup>7</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; <sup>8</sup>RTI, Rockville, Maryland; <sup>9</sup>*Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Corresponding author and reprints:

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RTI International Fax: (828) 254-6255  
3040 East Cornwallis Drive Email: mgantz@rti.org  
Research Triangle Park, NC 27709

Short title: Oxygen saturations and retinopathy of prematurity

Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute

ROP Secondary  
(07/11/2013)

**Word count**

Abstract: 145

Text: 2,786

**Abbreviations:**

AOR = Adjusted odds ratio

CI = Confidence interval

GA = Gestational age

IVH = Intraventricular hemorrhage

NEC = Necrotizing enterocolitis

PMA = Postmenstrual age

PVL = Periventricular leukomalacia

ROP = Retinopathy of prematurity

SGA = Small for gestational age

SpO<sub>2</sub> = Oxygen saturation

ROP Secondary  
(07/11/2013)

## ABSTRACT

### Objective

To identify specific oxygen saturation levels associated with severe ROP among infants in the SUPPORT trial.

### Study Design

Data on oxygen saturation and supplementation were collected up to 36 weeks postmenstrual age or to severe ROP determination for 984 surviving infants. Logistic regression models were created to predict severe ROP.

### Result

Percentage of days on supplemental oxygen (adjusted odds ratio (AOR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age (<10<sup>th</sup> percentile), severe illness (fraction of inspired oxygen >0.4 and on ventilator for >8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP.

### Conclusion

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

### Keywords

Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

ROP Secondary  
(07/11/2013)

## Introduction

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP decreased with exposure to restricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.<sup>1</sup> However, the resultant practice of uncontrolled restriction of oxygen supplementation, usually to no more than 50% inspired oxygen concentration, regardless of the degree of hypoxia created, and without the ability to monitor oxygenation continuously/tissue oxygen delivery was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup>

**Comment [mw3]:** In SUPPORT and in followup infants with severe ROP were not blind.

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval (CI) 0.37 – 0.73,  $p < 0.001$ , number needed to treat = 11), and the duration of oxygen supplementation among survivors was shorter.<sup>3</sup> However, a slight but unexpected increase in mortality was seen (x% vs Y%) increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.<sup>4</sup> An additional trial did not show any difference in mortality. (COT)

**Comment [mw4]:** Given the current controversies---need to be very careful and clear about the language.

Data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.<sup>6-8</sup> In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.<sup>7,11,12</sup> Although a

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**Comment [mw5]:** Would say it the other way around: within a narrow range of generally accepted oxygen saturation values it was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end.

**Comment [MG6]:** Wally: Correct?

**Comment [mw7]:** Would delete altogether. Not needed here.

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ROP Secondary  
(07/11/2013)

multicenter observational study did not report a significant association between partial pressure of oxygen ( $\text{PaO}_2$ ) levels and retinopathy,<sup>9</sup> a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels  $\geq 80\text{mmHg}$ .<sup>10</sup> While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets and about the specific oxygen saturation levels that are associated with ROP.

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Thus, ~~we sought to determine there is a need to determine~~ the oxygen saturation levels that were associated with severe ROP among survivors in the SUPPORT trials to assist in the selection of safe oxygen saturation targets that optimize survival but do not increase the risk of severe ROP. It was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end within a narrow range of generally accepted oxygen saturation values. In SUPPORT, infants were randomized to lower saturation targets (85-89%) versus higher saturation targets (91-95%) but as expected, the actual saturation levels achieved differed from those targeted and This is important because the actual oxygen saturation levels achieved differed from the targets in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably. Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities also are associated with a higher risk of severe ROP. This study tests the hypothesis that there are oxygen saturation levels that increase the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that duration of oxygen exposure, demographic characteristics, gestational age, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

Comment [WC8]: Quin J Nagadam study here

#### Subjects and Methods

ROP Secondary  
(07/11/2013)

This was a secondary analysis of the data from the oxygen saturation SUPPORT trial. As described previously,<sup>3</sup> surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks' postmenstrual age (PMA) and continued until the severe ROP outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group<sup>13,14</sup>) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, ~~both laser therapy and cryotherapy~~, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy.

Respiratory support data, including mode of support and fraction of inspired oxygen, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days of life through 36 weeks' PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life and every 6 hours thereafter through 36 weeks' PMA or death, transfer or discharge.

Oxygen saturation data were sampled every 10 seconds ~~were collected~~ while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks' PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant.

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Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, oxygen saturation ( $SpO_2$ ) values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value). Display, not actual,  $SpO_2$  values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some  $SpO_2$  values there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each  $SpO_2$  value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved. In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead.

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with  $SpO_2$  values of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

The percent of time spent at various  $SpO_2$  values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using chi-square and Wilcoxon rank sums tests. Both the total number of days and the percentage of days spent on supplemental oxygen up

ROP Secondary  
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to 36 weeks' PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at each SpO<sub>2</sub> value (<70%, 70%, 71%, ..., 100%) while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO<sub>2</sub> value that best discriminated between infants with and without severe ROP. This discriminant function was interpreted by measuring the correlation between it and the original percentages of time at each SpO<sub>2</sub> value.

SpO<sub>2</sub> values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP. Because of previous associations found between ROP and higher oxygen saturations, the percentages of time spent in the SpO<sub>2</sub> ranges of 96-100%, 97-100%, 98-100%, 99-100%, and 100% were also explored as predictors of severe ROP. Additional covariates were the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age (<10<sup>th</sup> percentile)<sup>4</sup> (SGA), any receipt of antenatal steroids, severe illness defined in SUPPORT as FiO<sub>2</sub> > 0.4 and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted carbon dioxide (CO<sub>2</sub>) in the first 14 days of life, periventricular leukomalacia (PVL), grade III or IV intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late-onset sepsis or meningitis. For PVL, severe IVH, NEC, and late-onset sepsis or meningitis, only morbidities that occurred before the date of severe ROP outcome determination were included.

**Comment [mw9]:** Need to justify this as a measure of severity of illness as it doesn't match anything a neonatologist would see as severe.

**Comment [WC10]:** This was pre-specified by the SUPPORT subcommittee

ROP Secondary  
(07/11/2013)

Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined and for the subset of infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. Due to the reduced number of infants available for the second analysis, the logistic regression model was reduced using backward selection, and only predictors that were statistically significant at the  $p < 0.05$  level were retained in the final model.

### Results

Of the 984 SUPPORT infants who survived to discharge and had the severe ROP ophthalmologic outcome determined, 132 (13%) were diagnosed with severe ROP. The median number of days on which supplemental oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54–74) and 43.5 for infants without severe ROP (IQR 18–63) (Wilcoxon rank sums test  $p < 0.001$ ). Ninety-five percent (125/132) of infants with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to 64% (541/852) of infants without severe ROP (chi-square  $p < 0.001$ ). Forty-five percent (60/132) of infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of infants without severe ROP (chi-square  $p < 0.001$ ). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP and 0.94 among those without severe ROP).

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had an ophthalmologic ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP. The distributions were similar for the two groups, particularly with respect to the median percent of time spent at each SpO<sub>2</sub> value. In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO<sub>2</sub> values less than 80%

Comment [mw11]: I understand what you mean but it will not make sense to readers outside of the trial.

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Comment [mw12]: not sure this helps me. Why included?

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Comment [WC13]: Is there a statistical test that we should do to prove that they are similar?

MG: I am working on whether I can do a statistical test comparing these distributions.

ROP Secondary  
(07/11/2013)

(correlations between the discriminant function and percentages of time at SpO<sub>2</sub> values <80% were all >0.5) (Figure 2). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks' PMA or severe ROP-ophthalmologic outcome determination was predictive of severe ROP (adjusted odds ratio (AOR) for a 5% increase in percent of days on supplemental oxygen: 1.14, 95% CI 1.06– 1.22, p<0.001), but percent of time while on supplemental oxygen with SpO<sub>2</sub><80% was not (AOR for a 5% increase in percent of time with SpO<sub>2</sub>< 80%:1.03, 95% CI 0.68– 1.56, p=0.89). Other significant predictors in the model were severe illness, late-onset sepsis or meningitis, GA, SGA, and clinical center (Table). When the percentages of time spent in SpO<sub>2</sub> ranges between 96% and 100% were investigated as predictors of severe ROP, none were statistically significant. When number of days was substituted for percent of days receiving supplemental oxygen, it did not reach significance as a predictor of severe ROP (AOR 1.02, 95% CI 0.999– 1.03, p=0.06); otherwise model results were similar.

Figure 3 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP-ophthalmologic outcome determination. The distributions were similar for infants with and without severe ROP, although infants with severe ROP spent a slightly higher percent of time with saturations near 100%. In multivariate analysis of this subset of infants, severe ROP was most highly associated with a greater percentage of time with an SpO<sub>2</sub> of 100% (correlation of 0.35 between discriminant function and percentage of time with SpO<sub>2</sub>=100%)(Figure 2). This variable was also significant in the logistic regression model to predict severe ROP (AOR for a 5% increase in percent of time with an SpO<sub>2</sub> of 100%:2.71, 95% CI 1.05– 6.96, p=0.04). Other significant predictors were severe illness, late-onset sepsis or meningitis, male gender, GA, and SGA (Table). When the percentage of time with an SpO<sub>2</sub> of 100% was replaced in the model by

**Comment [mw14]:** I am having great deal of difficulty understanding this. Needs more explanation and a very thorough legend. Severe ROP was highly assoc with Sat less than 80%????  
If this is stated correctly, need to discuss more thoroughly- why might this be???

**Comment [WC15]:** Statistical test needed to prove similarity?

MG: I am working on whether I can do a statistical test comparing these distributions.

**Comment [WC16]:** Significant? Do we need "slightly"?

MG: I am working on whether I can do a statistical test comparing these distributions.

ROP Secondary  
(07/11/2013)

percentages of time spent in other SpO<sub>2</sub> ranges between 96% and 100%, the ranges of 99-100% and 96-100% were statistically significant (AOR for a 5% increase in percent of time with SpO<sub>2</sub>99-100%: 1.68, 95% CI 1.02 – 2.77, p = 0.04; AOR for a 5% increase in percent of time with SpO<sub>2</sub>96-100%: 1.27, 95% CI 1.04 – 1.55, p = 0.02) (Figure 4) while estimates for other predictors in the model remained similar. Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup of infants.

### Discussion

Infants enrolled in SUPPORT who survived to discharge and were diagnosed with severe ROP spent significantly more time on supplemental oxygen on the days leading up to before 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to survivors without severe ROP. Logistic regression modeling showed that more time on oxygen was a significant risk factor for severe ROP after adjusting for baseline covariates. For infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination, a greater percentage of time with an oxygen saturation of 100% was a significant risk factor for severe ROP. The percentages of time spent in SpO<sub>2</sub> ranges of 99-100% and 96-100% were also statistically significant predictors, but the odds ratios decreased as the ranges expanded away from 100%. These results support the idea that the primary modifiable risk factors for severe ROP may be limited to avoiding extremely high oxygen saturations and reducing the amount of time spent on supplemental oxygen. Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).<sup>3</sup>

*[Need to add more interpretation of results.]*

A limitation of the study is that some oximeter data needed to be interpolated due to the lack of a one-to-one match between the skewed SpO<sub>2</sub> values displayed by the oximeters and actual saturations.

**Comment [WC17]:** How about other ranges (e.g. 97-100%, 96-99%, etc)? It is very important if these are NS.

MG: I want to avoid adding too many overlapping tests. What we have done so far is consistent with the analysis that was presented at PAS.

**Comment [mw18]:** What happened to the finding of sats < 80%...??

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However, this did not affect SpO<sub>2</sub> values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the SUPPORT oximeter data, the most likely impact of including time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

Other trials designed to target oxygen saturations similarly to SUPPORT have been completed<sup>5</sup> and could perform similar analyses. Previous large studies of associations of oxygen saturation levels and ROP reported targeted but not achieved saturations.<sup>7-9</sup>

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks' PMA is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination, less time spent on oxygen with an SpO<sub>2</sub> of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

**Comment [WC19]:** I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

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**Acknowledgements**

These should be brief, and should include sources of support including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially.

**Conflict of interest**

Authors must declare whether or not there are any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper. Conflict of interest should also be noted on the cover letter and as part of the submission process. See the Conflict of Interest documentation in the Editorial Policy section for detailed information.

ROP Secondary  
(07/11/2013)

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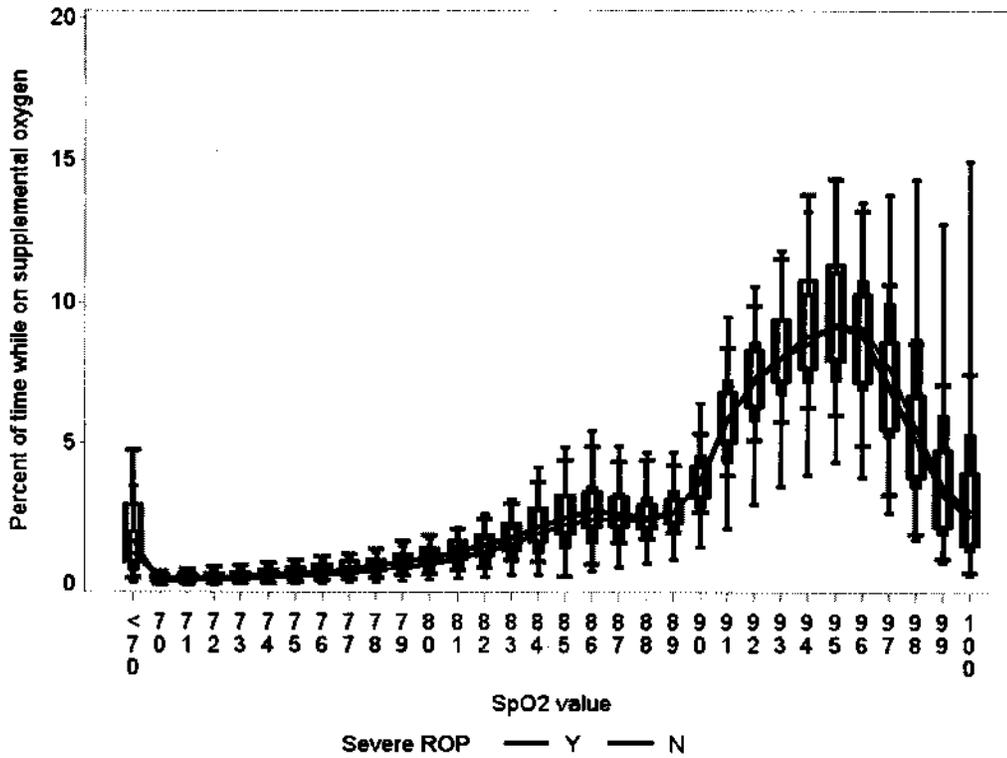
ROP Secondary  
(07/11/2013)

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Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination (N=932)

**Comment [WC20]:** I prefer to include interpretation of the results in figures legends also. Most journals use that style.

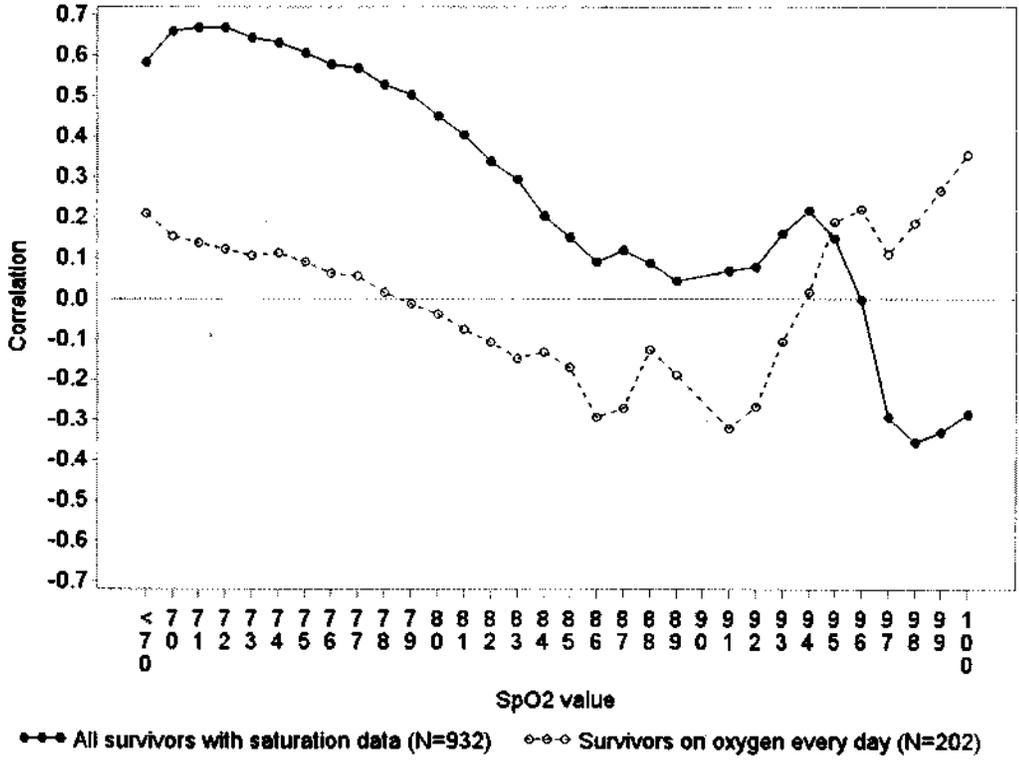


Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

ROP Secondary  
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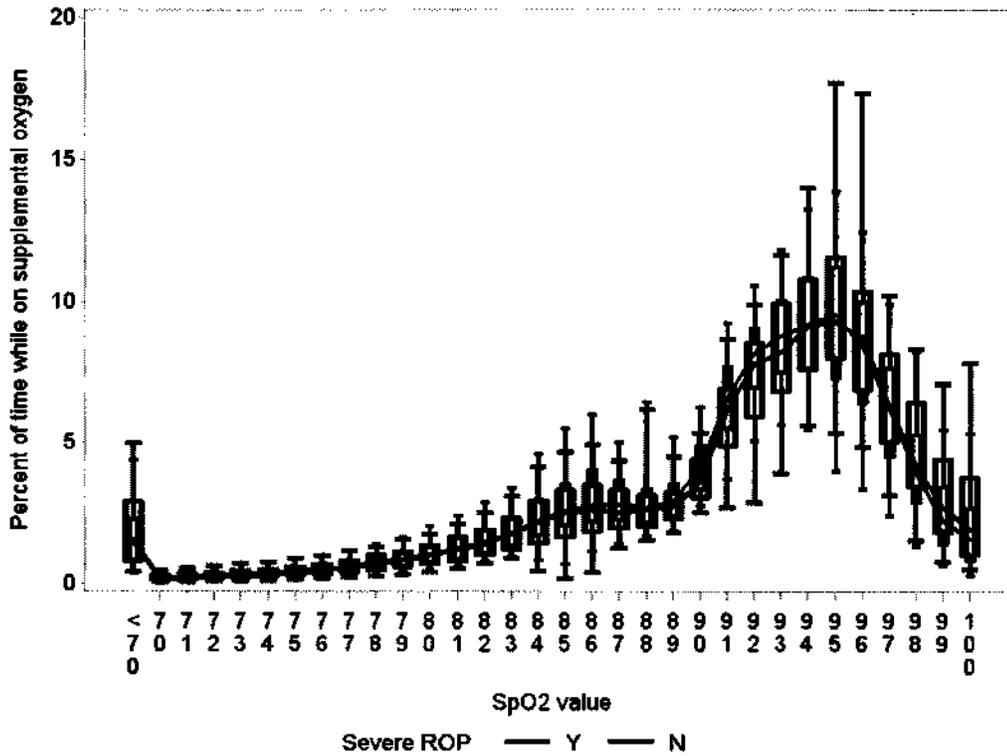
Figure 2. Correlation between discriminant functions from multivariate analyses and percentage of time spent at each SpO2 value while on supplemental oxygen: a measure of association between percentage of time spent at each SpO2 value and severe ROP

**Comment [MG21]:** I would be alright with getting rid of this figure if it seems confusing.



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Figure 3. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP - ophthalmologic outcome determination for infants who received oxygen each day (N=202)



Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

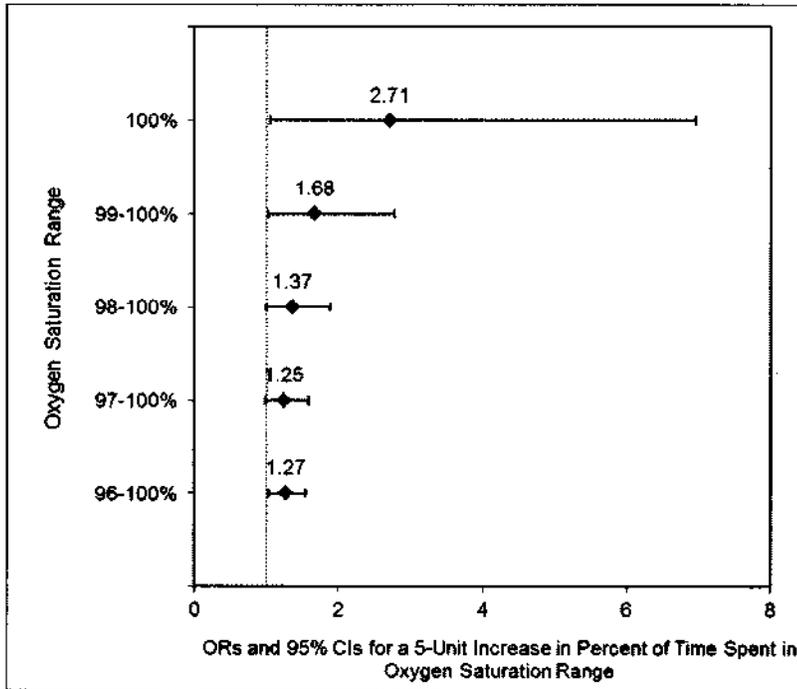
ROP Secondary  
(07/11/2013)

Table. Models predicting severe ROP among survivors to discharge

	Model for all survivors to discharge			Model for survivors who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome		
	Adjusted OR	Adjusted 95% CI	P value	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06 - 1.22)	<0.001			
Percent of time with SpO2<80% (unit=5% increase)	1.03	(0.68 - 1.56)	0.89			
Percent of time with SpO2=100% (unit=5% increase)				2.71	(1.05 - 6.96)	0.04
Severe illness	3.50	(2.05 - 5.97)	<0.001	2.48	(1.04 - 5.90)	0.04
Time weighted CO <sub>2</sub> in the first 14 days of life	0.99	(0.95 - 1.03)	0.60			
PVL	2.09	(0.83 - 5.28)	0.12			
IVH grade 3-4	1.10	(0.53 - 2.28)	0.79			
NEC	1.11	(0.53 - 2.30)	0.78			
Late-onset sepsis or meningitis	2.11	(1.31 - 3.39)	0.002	2.31	(1.13 - 4.72)	0.02
Any antenatal steroids	0.49	(0.13 - 1.92)	0.31			
Male	1.23	(0.77 - 1.96)	0.38	2.38	(1.13 - 5.00)	0.02
Gestational age (weeks)	0.49	(0.38 - 0.63)	<0.001	0.45	(0.30 - 0.68)	<0.001
Small for gestational age	2.38	(1.04 - 5.47)	0.04	4.06	(1.35 - 12.23)	0.01
Race/ethnicity (vs. Non-Hispanic White)			0.21			
Non-Hispanic Black	0.54	(0.30 - 0.99)				
Hispanic	0.89	(0.43 - 1.84)				
Other	1.16	(0.35 - 3.82)				
Center			0.15			

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(07/11/2013)

Figure 4. The effect of time spent in various oxygen saturation ranges in models predicting severe ROP among survivors to discharge who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome



**From:** Wally Carlo, M.D.  
**To:** [Finer, Neil](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kurt Schibler \[kurt.schibler@cchmc.org\]](#); [Abbot Laptook; Michele Walsh \(mcw3@cwru.edu\)](#); [Vaucher, Yvonne](#); [Myriam Peralta, M.D.](#); [Roger Faix \(Roger.Faix@hsc.utah.edu\)](#); [Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#); [mgantz@rti.org](#); [Abhik Das \(adas@rti.org\)](#); [dwallace@rti.org](#); [nxs5@case.edu](#); [Rich, Wade](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); ["Duara, Shahnaz" \(SDuara@med.miami.edu\)](#); [Cristina Navarrete \(CNavarrete@med.miami.edu\)](#)  
**Subject:** RE: Publications | Navarrete  
**Date:** Wednesday, July 24, 2013 8:01:25 AM

---

I agree with Neil that the focus should be growth.

Other outcomes should only be reported as they relate to growth.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
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-----Original Message-----

**From:** [Finer, Neil \[mailto:nfiner@ucsd.edu\]](#)  
**Sent:** Tuesday, July 23, 2013 7:22 PM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo, M.D.](#); [Kurt Schibler \[kurt.schibler@cchmc.org\]](#); [Abbot Laptook](#); [Michele Walsh \(mcw3@cwru.edu\)](#); [Vaucher, Yvonne](#); [Myriam Peralta, M.D.](#); [Roger Faix \(Roger.Faix@hsc.utah.edu\)](#); [Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#); [mgantz@rti.org](#); [Abhik Das \(adas@rti.org\)](#); [dwallace@rti.org](#); [nxs5@case.edu](#); [Rich, Wade](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); ["Duara, Shahnaz" \(SDuara@med.miami.edu\)](#); [Cristina Navarrete \(CNavarrete@med.miami.edu\)](#)  
**Subject:** Re: Publications | Navarrete

Hi Rose

Thanks for letting me review this manuscript I have made comments on the attached version I think that the discussion is overly lengthy, and that there is discussion of issues not related to growth - i.e. Severity of illness and death in this incomplete cohort I would also say the same about using quartiles of SpO2 - these areas should be more addressed by the overall cohort and not by incomplete subsets especially as the analyses are directed toward death.

We need to keep to the focus on growth and not over analyze this cohort for such outcomes Neil

On 7/12/13 9:39 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

>Hi

>Here is the SUPPORT Growth secondary paper. Please send your comments

>to Shahnaz and Tina (Copied on the cc line) by July 26.

>

>Thanks

>Rose

>

>Rosemary D. Higgins, MD

>Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal

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>

>-----Original Message-----

>From: Navarrete, Cristina [<mailto:CNavarrete@med.miami.edu>]

>Sent: Friday, July 12, 2013 12:17 PM

>To: Archer, Stephanie (NIH/NICHD) [E]

>Cc: 'Shahnaz Duara ([sduara@miami.edu](mailto:sduara@miami.edu))'; Higgins, Rosemary (NIH/NICHD)

>[E]

>Subject: RE: Publications | Navarrete

>

>Hello Stephanie!

>Here's the copy of the long overdue manuscript for review of the

>subcommittee.

>I apologise for the delay.

>Cristina

>

>>

**From:** Walsh, Michele  
**To:** Gantz, Marie; WCarlo@peds.uab.edu; nfiner@ucsd.edu; wrich@ucsd.edu; ROGER.FAIX@HSC.UTAH.EDU; Bradley.Yoder@hsc.utah.edu; nxs5@case.edu; ALaptook@WIHRI.org; Kurt.Schibler@cchmc.org; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT ROP/SpO2 secondary paper  
**Date:** Tuesday, July 23, 2013 4:29:44 PM  
**Attachments:** ROP secondary 2013-07-11 with notes mw comments.docx

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Overall: given the current environment, I think we need to be extremely careful in the wording of this paper and of the growth secondary. I have edited language with this cautious lens.

I have embedded comments in track change.

1. Some of the terminology could be altered to improve understanding

For example: timepoint of outcome determination: "36wks PMA or severe ROP determination"

Leads to long sentences with the phrase severe ROP three times. Suggest instead "36wks PMA or ophthalmologic determination"

2. Both papers need to provide some justification for the unusual definition of severe illness:  $FiO_2 > 0.4$  and  $> 8$ hrs of mechanical ventilation

In first 15 days. How was this determined? It will raise eyebrows. I suspect it was determined by some statistical cutpoint??

3. I do not understand Figure 2 and interpretation at all.

Also confused by one section in the results that references figure 2 and states:

"In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with  $SpO_2$  values less than 80% (correlations between the discriminant function and percentages of time at  $SpO_2$  values  $< 80\%$  were all  $> 0.5$ )."

This is not mentioned in the discussion and I do not understand what it means... seems to contradict the results of the main trial.

4. Can the horizontal axis in Figure 1 and Fig 3 be expanded to get the full number horizontally- or maybe just list every other number.

*Michele Walsh*

**Chief Division of Neonatology**

Rainbow Babies & Childrens Hospital

**Professor of Pediatrics**

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---

**From:** Gantz, Marie [mailto:mgantz@rti.org]

**Sent:** Thursday, July 11, 2013 2:26 PM

**To:** WCarlo@peds.uab.edu; nfiner@ucsd.edu; wrich@ucsd.edu; ROGER.FAIX@HSC.UTAH.EDU;

Bradley.Yoder@hsc.utah.edu; Walsh, Michele; nxs5@case.edu; ALaptook@WIHRI.org;

Kurt.Schibler@cchmc.org; Das, Abhik; higginsr@mail.nih.gov

**Subject:** SUPPORT ROP/SpO2 secondary paper

Hi all,

Attached is a long-overdue draft of the ROP/SpO2 secondary paper for SUPPORT. The target journal is J Perinatology. I would appreciate it if you would review and send comments/edits by July 26. Thanks in advance.

Marie

**Marie Gantz, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
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ROP Secondary  
(07/11/2013)

Oxygen Saturations and Retinopathy of Prematurity in Extremely Preterm Infants

**Comment [mw1]:** Suggest that title should say Baseline Oxygen Saturation or Actual Oxygen Saturations which will distinguish it from the secondary on intermittent hypoxia the Julie DiFiore and I are working on.

Marie G. Gantz, Ph.D.<sup>1</sup>; Waldemar A. Carlo, M.D.<sup>2</sup>; Neil N. Finer, M.D.<sup>3</sup>; Wade Rich, RRT<sup>3</sup>; Roger G. Faix, M.D.<sup>4</sup>; Bradley Yoder, M.D.<sup>4</sup>; Michele C. Walsh, M.D., M.S.<sup>5</sup>; Nancy Newman, R.N.<sup>5</sup>; Abbot Laptook, M.D.<sup>6</sup>; Kurt Schibler, M.D.<sup>7</sup>; Abhik Das, Ph.D.<sup>8</sup>; Rosemary D. Higgins, M.D.<sup>9</sup>; for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

<sup>1</sup>RTI International, Research Triangle Park, North Carolina; <sup>2</sup>University of Alabama at Birmingham, Birmingham, Alabama; <sup>3</sup>University of California, San Diego, San Diego, California; <sup>4</sup>University of Utah, Salt Lake City, Utah; <sup>5</sup>Case Western Reserve University, Cleveland, Ohio; <sup>6</sup>Women and Infants Hospital of Rhode Island, Providence, Rhode Island; <sup>7</sup>Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; <sup>8</sup>RTI, Rockville, Maryland; <sup>9</sup>*Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

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Research Triangle Park, NC 27709

Short title: Oxygen saturations and retinopathy of prematurity

Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute

ROP Secondary  
(07/11/2013)

Word count

Abstract: 145

Text: 2,786

Abbreviations:

AOR = Adjusted odds ratio

CI = Confidence interval

GA = Gestational age

IVH = Intraventricular hemorrhage

NEC = Necrotizing enterocolitis

PMA = Postmenstrual age

PVL = Periventricular leukomalacia

ROP = Retinopathy of prematurity

SGA = Small for gestational age

SpO<sub>2</sub> = Oxygen saturation

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**ABSTRACT**

**Objective**

To identify specific oxygen saturation levels associated with severe ROP among infants in the SUPPORT trial.

**Study Design**

Data on oxygen saturation and supplementation were collected up to 36 weeks postmenstrual age or to severe ROP determination for 984 surviving infants. Logistic regression models were created to predict severe ROP.

**Result**

Percentage of days on supplemental oxygen (adjusted odds ratio(AOR) for a 5% increase 1.14, 95% CI 1.06 – 1.22), center, lower gestational age, small for gestational age (<10<sup>th</sup> percentile), severe illness (fraction of inspired oxygen >0.4 and on ventilator for >8 consecutive hours in the first 14 days of life), and late onset sepsis or meningitis were predictors of severe ROP.

**Conclusion**

Among infants who survived to discharge, those with severe ROP spent significantly more time on oxygen supplementation.

**Keywords**

Infant Mortality, Newborn, Infant, Oximetry, Oxygen/administration & dosage, Oxygen Inhalation Therapy/adverse effects

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(07/11/2013)

## Introduction

Retinopathy of prematurity (ROP) is an important cause of blindness and other visual disabilities in preterm infants. The occurrence of ROP is indirectly proportional to gestational age, but high oxygen exposure has been associated with increased risk of retinopathy. The incidence of ROP decreased with exposure to restricted oxygen in preterm infants in randomized controlled trials performed in the 1950s.<sup>1</sup> However, the resultant practice of restricting oxygen supplementation, usually to no more than 50% inspired oxygen concentration, regardless of the degree of hypoxia created, and without the ability to monitor tissue oxygen delivery was estimated to result in an excess of 16 deaths per case of blindness prevented.<sup>2</sup>

**Comment [mw2]:** In SUPPORT and in followup infants with severe ROP were not blind.

In the SUPPORT trial, 1316 infants born at gestational ages of 24 0/7 weeks to 27 6/7 weeks between February 2005 and February 2009 were randomized to oxygen saturation target ranges of either 85-89% or 91-95%. Severe ROP among survivors was decreased in the lower (85-89%) oxygen saturation target group compared to the higher (91-95%) oxygen saturation target group (relative risk 0.52, 95% confidence interval (CI) 0.37 – 0.73,  $p < 0.001$ , number needed to treat = 11), and the duration of oxygen supplementation among survivors was shorter.<sup>3</sup> However, a slight but unexpected increase in mortality was seen (x% vs Y%) increased in the lower oxygen saturation group. Two similarly designed trials have been terminated prematurely due to similar mortality findings.<sup>5</sup> An additional trial did not show any difference in mortality. (COT)

**Comment [mw3]:** Given the current controversies—need to be very careful and clear about the language.

Data suggest that oxygen saturation levels previously thought to be in the upper limits of normal may increase the risk of ROP relative to low normal levels.<sup>6-8</sup> In three pre-post design studies, implementation of a policy of oxygen saturation targeting of approximately 83 to 95% was associated with a substantial reduction in retinopathy compared to the period before the policy, but actual oxygen saturations achieved, mortality, and neurodevelopmental outcomes were not reported.<sup>7,11,12</sup> Although a

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**Comment [mw4]:** Would say it the other way around: within a narrow range of generally accepted oxygen saturation values it was hoped that ROP would be decreased at the lower end of the spectrum compared to the higher end.

**Comment [MG5]:** Wally: Correct?

**Comment [mw6]:** Would delete altogether. Not needed here.

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ROP Secondary  
(07/11/2013)

multicenter observational study did not report a significant association between partial pressure of oxygen (PaO<sub>2</sub>) levels and retinopathy,<sup>9</sup> a single center cohort study using transcutaneous oxygen monitoring supported an association of increasing risk of retinopathy with exposure to arterial oxygen levels  $\geq$  80mmHg.<sup>10</sup> While data from these studies suggest that maintenance of oxygenation at ranges lower than previously used may decrease ROP, concerns remain about the safety of low oxygen saturation targets and about the specific oxygen saturation levels that are associated with ROP.

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Thus, ~~we sought to determine there is a need to determine~~ the oxygen saturation levels that were associated with severe ROP among survivors in the SUPPORT trial to assist in the selection of safe ~~oxygen saturation targets~~ that optimize survival but do not increase the risk of severe ROP. In SUPPORT infants were randomized to lower saturation targets (85-89%) versus higher saturation targets (91-95%) but the actual saturation levels achieved differed from those targeted and ~~This is important because the actual oxygen saturation levels achieved differed from the targets in SUPPORT, and the oxygen saturations while receiving oxygen supplementation of infants in the two treatment groups overlapped considerably.~~ Furthermore, it is likely that the overall duration of oxygen supplementation and other demographic characteristics and neonatal morbidities also are associated with a higher risk of severe ROP. This study tests the hypothesis that there are oxygen saturation levels that increase the risk of severe ROP independent of other baseline characteristics. It also tests the hypothesis that duration of oxygen exposure, demographic characteristics, gestational age, and neonatal morbidities will be associated with a higher risk of severe ROP independent of other characteristics.

#### Subjects and Methods

This was a secondary analysis of the data from the oxygen saturation SUPPORT trial. As described previously,<sup>3</sup> surviving infants were followed by ophthalmologists trained in the diagnosis of ROP. Examinations began by 33 weeks' postmenstrual age (PMA) and continued until the severe ROP

ROP Secondary  
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outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group<sup>13,14</sup>) was diagnosed if any of the following findings were present: in zone 1, stage 3 ROP, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of ROP; in zone 2, plus disease with stage 2 ROP or plus disease with stage 3 ROP. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. Severe retinopathy was defined as threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy.

Respiratory support data, including mode of support and fraction of inspired oxygen, were collected on study forms. Through February 2006, these data were collected every 8 hours during the first 14 days of life and once a day from 15 days of life through 36 weeks' PMA or death, transfer or discharge. After February 2006, respiratory support data were collected every two hours for the first 14 days of life and every 6 hours thereafter through 36 weeks' PMA or death, transfer or discharge.

Oxygen saturation data were sampled every 10 seconds ~~were collected~~ while infants were receiving oxygen supplementation. Use of the study pulse oximeters was discontinued at 36 weeks' PMA or when the infant had been without respiratory support for three days, whichever occurred earlier. However, if respiratory support was resumed prior to 36 weeks' PMA, the study oximeter was placed back on the infant.

Masking of treatment assignment was maintained using specially designed pulse oximeters with skewed display algorithms such that, for both treatment groups, oxygen saturation (SpO<sub>2</sub>) values in the correct target range were displayed as 88-92% (a maximum variation of 3% from the actual value).

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Display, not actual, SpO<sub>2</sub> values were recorded; thus, the data required transformation to actual saturation values prior to analysis. For some SpO<sub>2</sub> values there was not a one-to-one correspondence between display and actual values (specifically, for 84-85% and 93-96% in the low target group, 84-87% and 95-96% in the high target group). In these ranges, the number of seconds spent at each SpO<sub>2</sub> value was interpolated using a quadratic curve, ensuring that the total number of seconds was conserved. In cases where this method resulted in interpolation of a negative number of seconds, cubic Hermite interpolation, constrained to produce non-negative results, was used instead.

Oxygen saturations could only be targeted to assigned ranges while the infant was receiving supplemental oxygen. Furthermore, previous unpublished analyses of the SUPPORT pulse oximeter data revealed that infants spent more time with SpO<sub>2</sub> values of 97-100% on days when they did not receive supplemental oxygen compared to days on oxygen. For these reasons, this analysis included only those pulse oximeter data collected during oxygen supplementation. We considered the oximeter data to be for time on supplemental oxygen if the infant was receiving oxygen at the closest time point for which respiratory support data were collected on daily study forms. Pulse oximeter data from dates after the eye exam at which the ROP outcome (either severe ROP or resolution) was determined were excluded from this analysis.

The percent of time spent at various SpO<sub>2</sub> values while receiving supplemental oxygen was compared graphically for infants with and without severe ROP. The relationship between severe ROP and the amount of time spent on supplemental oxygen was explored using chi-square and Wilcoxon rank sums tests. Both the total number of days and the percentage of days spent on supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination were examined, and the Pearson correlation between the two measures was assessed.

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Exploratory multivariate analysis was used to assess the relationship between severe ROP and the percent of time spent at each SpO<sub>2</sub> value (<70%, 70%, 71%, ..., 100%) while on oxygen supplementation. The result of this analysis was a linear combination of the percentages of time at each SpO<sub>2</sub> value that best discriminated between infants with and without severe ROP. This discriminant function was interpreted by measuring the correlation between it and the original percentages of time at each SpO<sub>2</sub> value.

SpO<sub>2</sub> values found to be most highly associated with severe ROP in the multivariate analyses were included as covariates in logistic regression models predicting severe ROP. Because of previous associations found between ROP and higher oxygen saturations, the percentages of time spent in the SpO<sub>2</sub> ranges of 96-100%, 97-100%, 98-100%, 99-100%, and 100% were also explored as predictors of severe ROP. Additional covariates were the amount of time spent on supplemental oxygen (both the number of days and percent of days on oxygen were evaluated as potential predictors) and demographic and neonatal characteristics. Selection of demographic and neonatal characteristics was based on possible association with ROP and included clinical center, gender, race/ethnicity, gestational age (GA), small for gestational age (<10<sup>th</sup> percentile)<sup>4</sup> (SGA), any receipt of antenatal steroids, severe illness defined as FiO<sub>2</sub> > 0.4 and being on a ventilator for > 8 consecutive hours in the first 14 days of life, time weighted carbon dioxide (CO<sub>2</sub>) in the first 14 days of life, periventricular leukomalacia (PVL), grade III or IV intraventricular hemorrhage (severe IVH), necrotizing enterocolitis (NEC), and late-onset sepsis or meningitis. For PVL, severe IVH, NEC, and late-onset sepsis or meningitis, only morbidities that occurred before the date of severe ROP outcome determination were included.

**Comment [mw7]:** Need to justify this as a measure of severity of illness as it doesn't match anything a neonatologist would see as severe.

Separate analyses were conducted for all infants who survived to discharge and had a severe ROP outcome determined and for the subset of infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination. Due to the reduced number of infants

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available for the second analysis, the logistic regression model was reduced using backward selection, and only predictors that were statistically significant at the  $p < 0.05$  level were retained in the final model.

### Results

Of the 984 SUPPORT infants who survived to discharge and had the severe-ROP ophthalmologic outcome determined, 132 (13%) were diagnosed with severe ROP. The median number of days on which supplemental oxygen was received was 67 for infants with severe ROP (interquartile range (IQR) 54–74) and 43.5 for infants without severe ROP (IQR 18–63) (Wilcoxon rank sums test  $p < 0.001$ ). Ninety-five percent (125/132) of infants with severe ROP received supplemental oxygen on at least half of the days prior to 36 weeks' PMA or severe-ROP ophthalmologic outcome determination compared to 64% (541/852) of infants without severe ROP (chi-square  $p < 0.001$ ). Forty-five percent (60/132) of infants with severe ROP received supplemented oxygen every day compared to 17% (142/852) of infants without severe ROP (chi-square  $p < 0.001$ ). The correlation between number of days and percent of days with supplemental oxygen was high (0.82 among those with severe ROP and 0.94 among those without severe ROP).

Ninety-five percent (932/984) of SUPPORT infants who survived to discharge and had a ophthalmologic ROP outcome determined had oxygen saturation data available. Figure 1 compares the percent of time spent at each SpO<sub>2</sub> value while receiving supplemental oxygen for infants with and without severe ROP. The distributions were similar for the two groups, particularly with respect to the median percent of time spent at each SpO<sub>2</sub> value. In multivariate analysis, severe ROP was most highly associated with percentages of time while on supplemental oxygen with SpO<sub>2</sub> values less than 80% (correlations between the discriminant function and percentages of time at SpO<sub>2</sub> values  $< 80\%$  were all  $> 0.5$ ) (Figure 2). In logistic regression analysis adjusted for other risk factors, percent of days on supplemental oxygen prior to 36 weeks' PMA or severe-ROP ophthalmologic outcome determination

Comment [mw8]: I understand what you mean but it will not make sense to readers outside of the trial.

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Comment [mw9]: not sure this helps rae. Why included?

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Comment [WC10]: Is there a statistical test that we should do to prove that they are similar?

MG: I am working on whether I can do a statistical test comparing these distributions.

Comment [mw11]: I am having great deal of difficulty understanding this. Needs more explanation and a very thorough legend. Severe ROP was highly assoc with Sat less than 80%?%?%???? If this is stated correctly, need to discuss more thoroughly- why might this be???

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was predictive of severe ROP (adjusted odds ratio (AOR) for a 5% increase in percent of days on supplemental oxygen: 1.14, 95% CI 1.06– 1.22,  $p < 0.001$ ), but percent of time while on supplemental oxygen with  $SpO_2 < 80\%$  was not (AOR for a 5% increase in percent of time with  $SpO_2 < 80\%$ : 1.03, 95% CI 0.68– 1.56,  $p = 0.89$ ). Other significant predictors in the model were severe illness, late-onset sepsis or meningitis, GA, SGA, and clinical center (Table). When the percentages of time spent in  $SpO_2$  ranges between 96% and 100% were investigated as predictors of severe ROP, none were statistically significant. When number of days was substituted for percent of days receiving supplemental oxygen, it did not reach significance as a predictor of severe ROP (AOR 1.02, 95% CI 0.999– 1.03,  $p = 0.06$ ); otherwise model results were similar.

Figure 3 compares the percent of time spent at each  $SpO_2$  value while receiving supplemental oxygen for infants with and without severe ROP among the 202 infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination. The distributions were similar for infants with and without severe ROP, although infants with severe ROP spent a slightly higher percent of time with saturations near 100%. In multivariate analysis of this subset of infants, severe ROP was most highly associated with a greater percentage of time with an  $SpO_2$  of 100% (correlation of 0.35 between discriminant function and percentage of time with  $SpO_2 = 100\%$ ) (Figure 2). This variable was also significant in the logistic regression model to predict severe ROP (AOR for a 5% increase in percent of time with  $SpO_2$  of 100%: 2.71, 95% CI 1.05– 6.96,  $p = 0.04$ ). Other significant predictors were severe illness, late-onset sepsis or meningitis, male gender, GA, and SGA (Table). When the percentage of time with an  $SpO_2$  of 100% was replaced in the model by percentages of time spent in other  $SpO_2$  ranges between 96% and 100%, the ranges of 99–100% and 96–100% were statistically significant (AOR for a 5% increase in percent of time with  $SpO_2$  99–100%: 1.68, 95% CI 1.02 – 2.77,  $p = 0.04$ ; AOR for a 5% increase in percent of time with  $SpO_2$  96–100%: 1.27, 95%

**Comment [WC12]:** Statistical test needed to prove similarity?

MG: I am working on whether I can do a statistical test comparing these distributions

**Comment [WC13]:** Significant? Do we need "slightly"?

MG: I am working on whether I can do a statistical test comparing these distributions.

**Comment [WC14]:** How about other ranges (e.g. 97–100%, 96–99%, etc)? It is very important if these are NS

MG: I want to avoid adding too many overlapping tests. What we have done so far is consistent with the analysis that was presented at PAS.

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CI 1.04 – 1.55,  $p = 0.02$ ) (Figure 4) while estimates for other predictors in the model remained similar. Number of days receiving supplemental oxygen was not a significant predictor of severe ROP in this subgroup of infants.

### Discussion

Infants enrolled in SUPPORT who survived to discharge and were diagnosed with severe ROP spent significantly more time on supplemental oxygen on the days leading up to before 36 weeks' PMA or severe ROP ophthalmologic outcome determination compared to survivors without severe ROP.

Logistic regression modeling showed that more time on oxygen was a significant risk factor for severe ROP after adjusting for baseline covariates. For infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP ophthalmologic outcome determination, a greater percentage of time with an oxygen saturation of 100% was a significant risk factor for severe ROP. The percentages of time spent in SpO<sub>2</sub> ranges of 99-100% and 96-100% were also statistically significant predictors, but the odds ratios decreased as the ranges expanded away from 100%. These results support the idea that the primary modifiable risk factors for severe ROP may be limited to avoiding extremely high oxygen saturations and reducing the amount of time spent on supplemental oxygen. Notably, surviving infants in the SUPPORT trial who were randomized to a lower oxygen saturation target (85-89%) spent fewer days on supplemental oxygen compared to those randomized to a higher oxygen saturation target (91-95%).<sup>3</sup>

*[Need to add more interpretation of results.]*

A limitation of the study is that some oximeter data needed to be interpolated due to the lack of a one-to-one match between the skewed SpO<sub>2</sub> values displayed by the oximeters and actual saturations. However, this did not affect SpO<sub>2</sub> values below 84% or above 96% which were of greatest interest in this analysis. Another limitation is that oximeter data for time on supplemental oxygen were identified based on the closest time point at which respiratory support data were captured on study forms. As

**Comment [mw15]:** What happened to the finding of sats < 80%...??

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respiratory support data were not continuously reported, it is possible that some oximeter data for times when the infants were not actually receiving supplemental oxygen were included in this analysis. Based on previous unpublished analyses of the SUPPORT oximeter data, the most likely impact of including time not on oxygen support would be an increase in oximeter readings with oxygen saturations near 100%.

Other trials designed to target oxygen saturations similarly to SUPPORT have been completed<sup>5</sup> and could perform similar analyses. Previous large studies of associations of oxygen saturation levels and ROP reported targeted but not achieved saturations.<sup>7,9</sup>

In conclusion, a greater proportion of days with receipt of supplemental oxygen prior to 36 weeks' PMA is one of the strongest predictors of severe ROP. Severe pulmonary disease, late-onset sepsis or meningitis, PVL, SGA, lower GA, and center were other predictors of severe ROP. Among infants who received supplemental oxygen every day up to 36 weeks' PMA or severe ROP outcome determination, less time spent on oxygen with an SpO<sub>2</sub> of 100% was associated with a decrease in severe ROP. These results support the concept that infants with prolonged oxygen need are at high risk for severe ROP. This effect is larger than the effects of time spent in specific oxygen saturation ranges.

**Comment [WC16]:** I have to read more papers on the subject to put our results in perspective of the most pertinent literature.

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**Acknowledgements**

These should be brief, and should include sources of support including sponsorship (e.g. university, charity, commercial organization) and sources of material (e.g. novel drugs) not available commercially.

**Conflict of interest**

Authors must declare whether or not there is any competing financial interests in relation to the work described. This information must be included at this stage and will be published as part of the paper. Conflict of interest should also be noted on the cover letter and as part of the submission process. See the Conflict of Interest documentation in the Editorial Policy section for detailed information.

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(07/11/2013)

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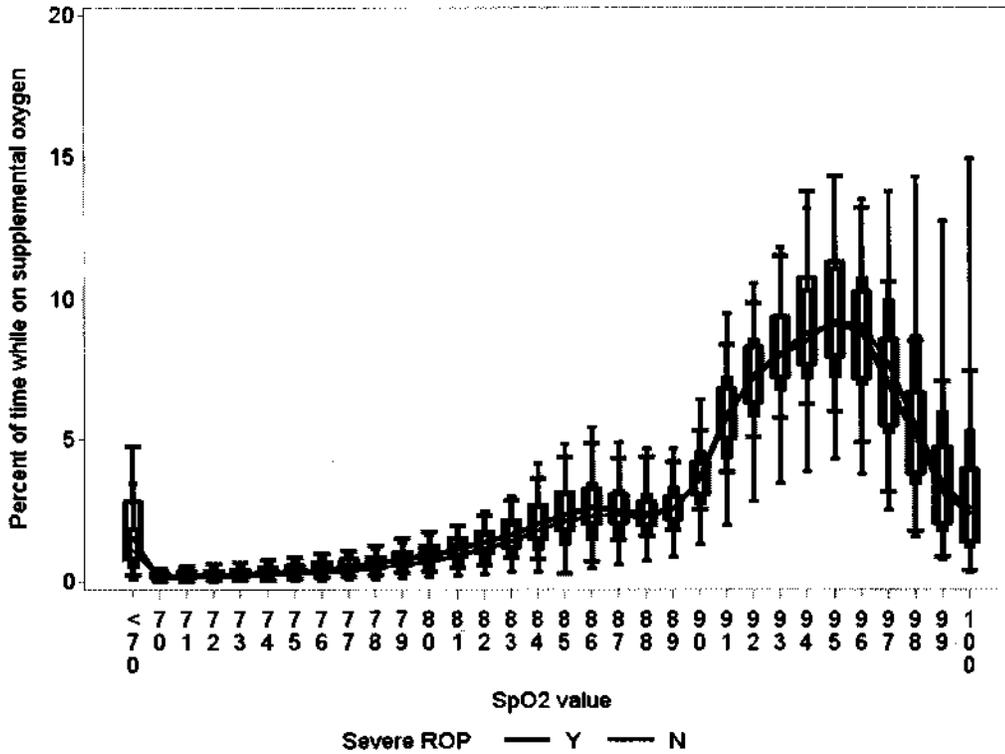
**ROP Secondary  
(07/11/2013)**

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ROP Secondary  
(07/11/2013)

Figure 1. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA or severe ROP outcome determination (N=932)

**Comment [WC17]:** I prefer to include interpretation of the results in figures legends also. Most journals use that style.

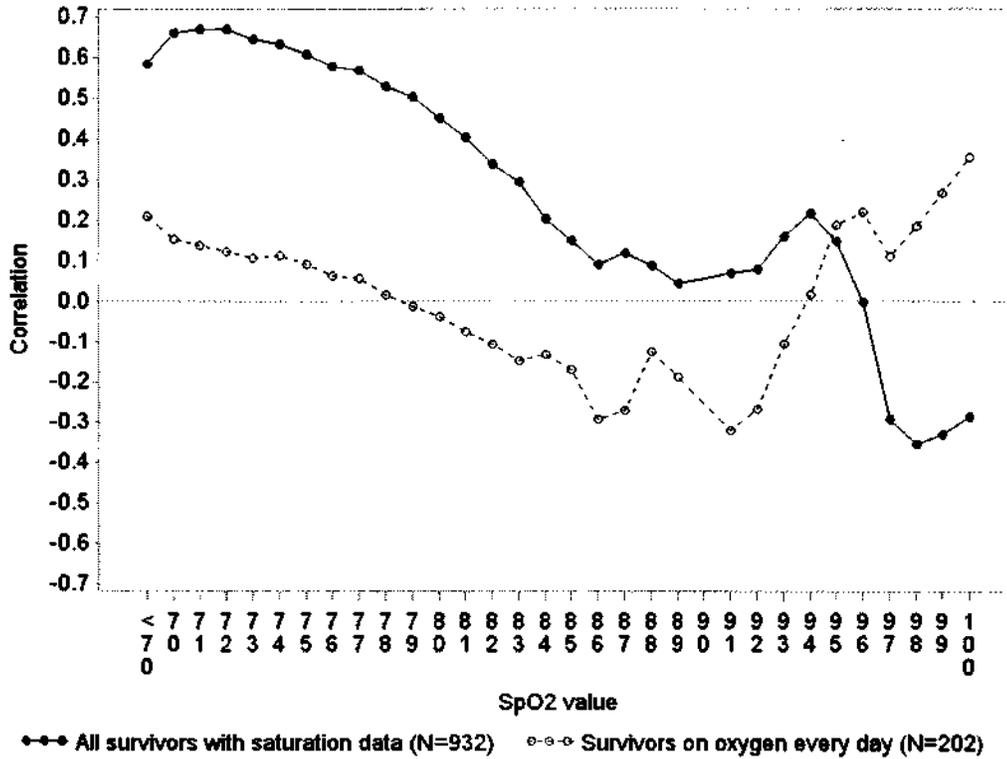


Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

ROP Secondary  
(07/11/2013)

Figure 2. Correlation between discriminant functions from multivariate analyses and percentage of time spent at each SpO2 value while on supplemental oxygen: a measure of association between percentage of time spent at each SpO2 value and severe ROP

Comment [MG18]: I would be alright with getting rid of this figure if it seems confusing.

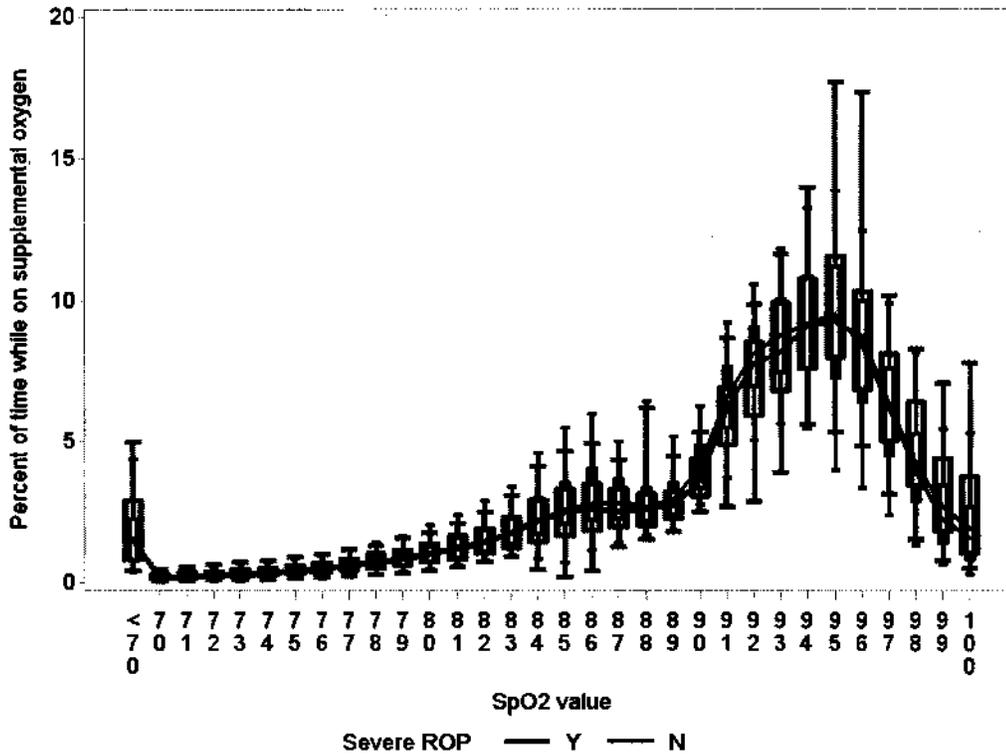


ROP Secondary  
(07/11/2013)

Figure 3. Distribution of oxygen saturations while receiving supplemental oxygen up to 36 weeks' PMA

or severe ROP - ophthalmologic outcome determination for infants who received oxygen each

day(N=202)



Boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles. Whiskers represent 5<sup>th</sup> to 95<sup>th</sup> percentiles. Lines connecting the boxes represent medians.

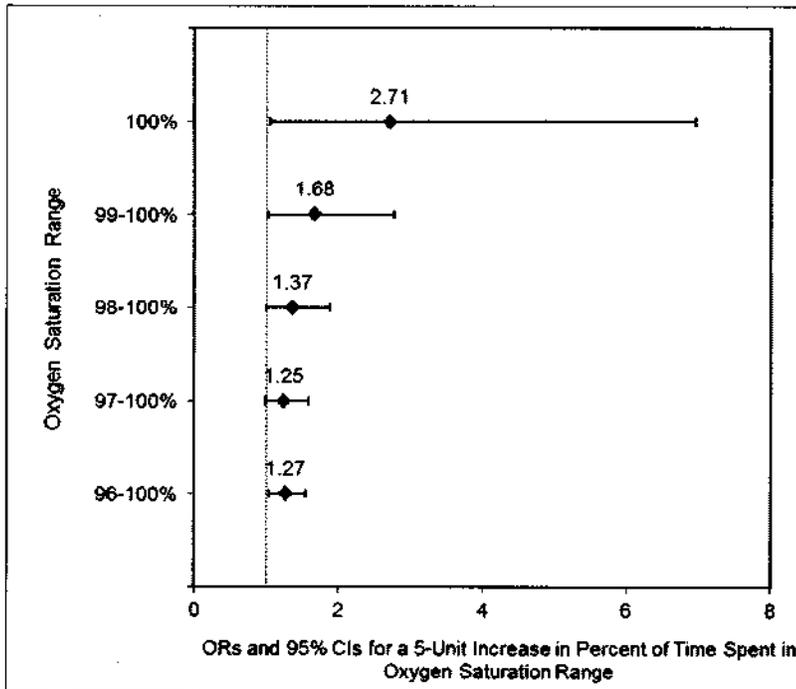
ROP Secondary  
(07/11/2013)

Table. Models predicting severe ROP among survivors to discharge

	Model for all survivors to discharge			Model for survivors who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome		
	Adjusted OR	Adjusted 95% CI	P value	Adjusted OR	Adjusted 95% CI	P value
Percent of days on oxygen (unit=5% increase)	1.14	(1.06 – 1.22)	<0.001			
Percent of time with SpO2<80% (unit=5% increase)	1.03	(0.68 – 1.56)	0.89			
Percent of time with SpO2=100% (unit=5% increase)				2.71	(1.05 – 6.96)	0.04
Severe illness	3.50	(2.05 – 5.97)	<0.001	2.48	(1.04 – 5.90)	0.04
Time weighted CO <sub>2</sub> in the first 14 days of life	0.99	(0.95 – 1.03)	0.60			
PVL	2.09	(0.83 – 5.28)	0.12			
IVH grade 3-4	1.10	(0.53 – 2.28)	0.79			
NEC	1.11	(0.53 – 2.30)	0.78			
Late-onset sepsis or meningitis	2.11	(1.31 – 3.39)	0.002	2.31	(1.13 – 4.72)	0.02
Any antenatal steroids	0.49	(0.13 – 1.92)	0.31			
Male	1.23	(0.77 – 1.96)	0.38	2.38	(1.13 – 5.00)	0.02
Gestational age (weeks)	0.49	(0.38 – 0.63)	<0.001	0.45	(0.30 – 0.68)	<0.001
Small for gestational age	2.38	(1.04 – 5.47)	0.04	4.06	(1.35 – 12.23)	0.01
Race/ethnicity (vs. Non-Hispanic White)			0.21			
Non-Hispanic Black	0.54	(0.30 – 0.99)				
Hispanic	0.89	(0.43 – 1.84)				
Other	1.16	(0.35 – 3.82)				
Center			0.15			

ROP Secondary  
(07/11/2013)

Figure 4. The effect of time spent in various oxygen saturation ranges in models predicting severe ROP among survivors to discharge who received supplemental oxygen every day up to 36 weeks' PMA or ROP outcome



**From:** Walsh, Michele  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; nfiner@ucsd.edu; kurt.schibler@cchmc.org; Abbot Laptook; mcw3@cwru.edu; Yvonne Vaucher; mperalta@peds.uab.edu; Roger.Faix@hsc.utah.edu; Bradley.yoder@hsc.utah.edu; Gantz, Marie; Wallace, Dennis; nxs5@case.edu; Wade Rich  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; SDuara@med.miami.edu; CNavarrete@med.miami.edu; Wrage, Lisa Ann  
**Subject:** RE: Publications | Navarrete  
**Date:** Tuesday, July 23, 2013 2:39:23 PM  
**Attachments:** Manuscript Growth Outcomes SUPPORT 7 2013 AD MW comments.docx

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I added my comments to those of Abhik in track change.  
Adjustment to analyses by severity of illness need to better explained.  
Also: need to be careful with the analyses by saturation quartile to  
Not overlap and not contradict the secondary saturation analysis by Marie Gantz.

Michele Walsh  
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-----Original Message-----

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Tuesday, July 16, 2013 4:36 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; nfiner@ucsd.edu; kurt.schibler@cchmc.org; Abbot Laptook; mcw3@cwru.edu; Yvonne Vaucher; mperalta@peds.uab.edu; Roger.Faix@hsc.utah.edu; Bradley.yoder@hsc.utah.edu; Gantz, Marie; Wallace, Dennis; nxs5@case.edu; Wade Rich  
Cc: Archer, Stephanie (NIH/NICHD) [E]; SDuara@med.miami.edu; CNavarrete@med.miami.edu; Wrage, Lisa Ann  
Subject: RE: Publications | Navarrete

Here are my comments.

Thanks

Abhik

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

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, July 12, 2013 12:40 PM  
To: Wally Carlo, M.D.; nfiner@ucsd.edu; Kurt Schibler [kurt.schibler@cchmc.org]; Abbot Laptook; Michele Walsh (mcw3@cwru.edu); Yvonne Vaucher; mperalta@peds.uab.edu; Roger Faix (Roger.Faix@hsc.utah.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Gantz, Marie; Das, Abhik; Wallace, Dennis; nxs5@case.edu; Wade Rich  
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Duara, Shahnaz' (SDuara@med.miami.edu); Cristina Navarrete (CNavarrete@med.miami.edu)  
Subject: FW: Publications | Navarrete

Hi

Here is the SUPPORT Growth secondary paper. Please send your comments to Shahnaz and Tina (Copied on the cc line) by July 26.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
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-----Original Message-----

From: Navarrete, Cristina [<mailto:CNavarrete@med.miami.edu>]  
Sent: Friday, July 12, 2013 12:17 PM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Cc: 'Shahnaz Duara ([sduara@miami.edu](mailto:sduara@miami.edu))'; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Publications | Navarrete

Hello Stephanie!  
Here's the copy of the long overdue manuscript for review of the subcommittee.  
I apologise for the delay.  
Cristina

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**Growth Outcomes of Preterm Infants Exposed to  
Different Oxygen Saturation Target Ranges from Birth**

Cristina T Navarrete<sup>1</sup>, Lisa A Wraga<sup>2</sup>, Shahnaz Duara<sup>1</sup>, on behalf of the SUPPORT  
Subcommittee for the NICHD Neonatal Research Network. University of Miami, Miami, FL<sup>1</sup>;  
Research Triangle Institute International, RTP, NC<sup>2</sup>; NICHD, Rockville, MD

Abstract:

**BACKGROUND:** Post-natal growth restriction is a major morbidity in preterm infants.

Perturbations in oxygenation may influence somatic growth; a recent observational study showed that infants exposed to higher oxygen saturation (SpO<sub>2</sub>) targets experience poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that the lower target range of SpO<sub>2</sub> from birth, as compared to the higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carlo, NEJM 2010). However, it is not known ~~what the impact of whether~~ assignment to these different saturation targets immediately after birth would have any impact on postnatal growth.

**OBJECTIVE:** To test the hypotheses that infants maintained in the lower SpO<sub>2</sub> target range while on supplemental oxygen from birth will have better growth at 36 weeks post-menstrual age (PMA) and at 18-22 months corrected age (CA) (fewer babies <10<sup>th</sup> percentile% for weight), and better growth trajectories from birth to 18-22 months CA.

**METHODS:** A sub-group of 810 preterm infants from the SUPPORT trial, randomized at birth to lower (85-89%, n=402, GA 26.2 ± 1.1 wks, BW 838.6 ± 186 gm) ~~and or~~ higher (91-95%, n=408, GA 26.2 ± 1.1 wks, BW 839.6 ± 191 gm) SpO<sub>2</sub> target ranges were studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28; 32 and 36 weeks PMA, and at 18-22 months corrected age. Growth velocities were estimated for each randomization group using the exponential method, and analyzed using linear mixed models. Poor growth outcome, defined

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as weight < 10<sup>th</sup> %ile at 36 weeks PMA and 18-22 months CA, was ~~analyzed compared across the two treatment groups~~ using robust Poisson regression.

RESULTS: Growth ~~outcomes including growth at 36 weeks PMA and 18-22 months CA, as well as growth velocity~~ was ~~were~~ not different between the lower and higher SpO<sub>2</sub> target groups. ~~In this large subgroup, mortality was not different between groups at 36 weeks PMA and both, growth at 36 wks PMA and at 18-22 month were not different between the two groups.~~

CONCLUSION: Early oxygen saturation targeting in the standard of care range did not impact growth velocity or growth failure in preterm infants receiving supplemental oxygen in accordance to ~~with~~ the requirements of ~~the~~ SUPPORT trial.

**Comment [AD1]:** I strongly feel that we should not get into the mortality issue here because (a) it was not a stated outcome for this study, and (b) we don't want to contradict our own findings from the main trial.

### Introduction:

The improved survival of extremely low gestational age infants highlights a new problem, the significant incidence of growth restriction seen around the age of term equivalence<sup>1</sup> that persists until later in childhood<sup>2</sup>. The incidence of postnatal growth restriction (weight less than the tenth percentile for postmenstrual age at the time of hospital discharge) has been described to range anywhere from 79%<sup>1</sup> to 99%<sup>3</sup>, when using fetal-infant growth curves. The consequence of poor growth includes poorer neuro-developmental outcome<sup>2,4</sup> as well as an increased risk in adulthood for metabolic syndrome and type 2 diabetes if there is subsequent catch-up growth<sup>5</sup>.

The recent emphasis on the provision of early and adequate nutritional support recognizes the connection between nutrition and growth<sup>6-8</sup>. However, when Embleton *et al* followed infants prospectively, they were able to attribute only 45% of variance in weight gain to energy intake deficits<sup>9</sup>, suggesting that postnatal growth is influenced by factors beyond caloric intake. Tissue oxygenation has often been postulated to be amongst these factors<sup>10-15</sup>. Animal studies investigating this possibility have shown species-specific outcomes, with rat pups raised in hypoxic conditions after birth showing a reduced body mass, while hamster pups raised in the same condition have growth unaffected<sup>10</sup>. In humans, the relationship between oxygenation and postnatal growth is still not fully understood. Infants with established bronchopulmonary dysplasia (BPD) have slower growth velocities when weaned off supplemental oxygen at discharge<sup>11, 12</sup>; whereas those discharged on home oxygen have either better growth<sup>13, 14</sup> or no difference in growth<sup>15</sup>. For preterm infants without BPD, assignment to different saturation targets starting several weeks after birth did not impact later growth<sup>16, 17</sup>. On retrospective observation of neonatal units with differing oxygen saturation targeting policies,

infants in the neonatal intensive care unit(NICU) with lower saturation targets incidentally had better in-hospital growth<sup>18</sup>, suggesting that higher oxygen saturation may play in role in creating postnatal growth restriction. The design of the NICHD Neonatal Research Network (NRN) Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial(SUPPORT) offered an opportunity to investigate this possibility in a randomized and controlled fashion from the time of birth, which is something that has never been done before<sup>19,20</sup>. We hypothesized that infants enrolled in SUPPORT assigned to the lower saturation target group would have better growth velocity and less growth failure in hospital and at 18-22 months corrected age.

Methods:

Sample: Our sample is composed of a subgroup of infants enrolled in SUPPORT, a prospective 2 x 2 factorial, randomized trial. The oxygen saturation targeting arm of SUPPORT was designed to determine whether exposure to a lower saturation target soon after birth, within the accepted normal range at the time, was associated with a lower incidence of severe retinopathy of prematurity and/or death before discharge from the hospital. Between February 2005 and February 2009, women delivering between 24 weeks 0 days and 27 weeks 6 days of gestation were asked to enroll in the study at participating centers. Infants were randomized to either lower (85-89%) or higher (91-95%) saturation target arms within the accepted oxygen saturation range the first two hours after birth. Electronically altered pulse oximeters (Massimo™), for masking, were used for both groups until 36 weeks postmenstrual age (PMA) or until the infant was breathing ambient air and off positive pressure support for more than 72 hours.

**Comment [AD2]:** Should we mention that this was not an intentional subgroup, but just a product of the timing of approval for this secondary study?  
MW: yes would add this.

This study protocol was approved by the institutional review board of all the 15 participating centers, and written informed consent was obtained from each infant's parent/guardian before any measurements were taken for analysis. In addition to the patient descriptors collected in the main trial<sup>19</sup>, select anthropometric measurements and nutrition snapshots were collected by research nurses at each institution. Measurements were obtained at birth, weekly for the first 4 weeks, and again at 32 and 36 weeks PMA and 18-22 month follow-up, if the infant was deemed stable; weight was obtained using the bedside scale, length was measured using the Preemie Length Board<sup>TM</sup> and head circumference was measured using a tape measure. Each measurement was obtained twice and then averaged. Detailed 24-hour nutritional data were collected weekly for the first 4 weeks and then at 32 and 36 weeks PMA by chart review at time of discharge. Type and volume of intravenous solutions, including composition of parenteral nutrition, and type and volume of enteral feedings, including modular additives, were recorded. Composition of milk formula and breastmilk (mother's own or donor) was based on the assumed average composition of breastmilk and the manufacturer's product information for the various milk formulas. Research nurses used standardized study forms while collecting information and all data were subsequently transmitted to the central NRN data-coordinating center at RTI International.

The primary outcome measures were the combined outcome of growth failure, defined as weight less than 10<sup>th</sup> percentile, or death, at 36 weeks PMA and at 18-22 month follow-up, and in-hospital growth velocities. The reference growth standards used were the gender-specific intrauterine growth curves of Olsen<sup>21</sup> for in-hospital growth and the WHO Growth Curves<sup>22</sup> for 18-22 month growth.

**Comment [AD3]:** Did we just look at in-hospital velocities and not up to 18-22 months? This seems to be contradicted in the next sentence.

**Comment [mw4]:** ?corrected for PMA?

Statistical Analysis: Clinical characteristics and outcomes for infants in the higher and lower oxygen saturation target groups were compared using linear mixed models for continuous variables and robust Poisson regression for binary outcomes, adjusting for multiple birth clustering and SUPPORT trial stratification variables (gestational age group and center). An unadjusted Wilcoxon rank sum test was used for skewed continuous variables. In-hospital growth velocity was calculated using the exponential method<sup>23</sup>. Post-hoc analysis of actual median saturations while on supplemental oxygen allowed the study population as a whole to be divided into quartiles and assessed for mortality and growth. Severity of illness (defined as  $\text{FiO}_2 > 0.4$  and mechanical ventilation for more than 8 hours in the first 15 days) according to quartile of actual median saturation was analyzed by Chi-square tests. Primary outcomes were analyzed by quartile using robust Poisson regression with results expressed as adjusted relative risks and 95% confidence intervals. All analyses were performed using SAS version 9.3 at RTI International.

#### Results:

A total of 1,316 infants were enrolled in SUPPORT (FIGURE 1); of these, 810 infants were enrolled in the Growth Secondary Study. Of the enrolled infants, 681 infants survived to 36 weeks PMA or discharge (whichever came first) and 609 infants returned for follow-up at 18-22 months corrected age. Only 535 infants had data available for the calculation of in-hospital growth velocity, at 36 weeks PMA or discharge, due to incomplete data collection for the rest (n = 146).

Characteristics of the Study Sample: The baseline characteristics of the lower and the higher saturation groups, including the anthropometric measures, were similar (TABLE 1). The means for individual anthropometric measures (weight, length and head circumference), at

Comment [AD5]: Need to define what these are.

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Comment [mw6]: Need to be careful: this overlaps a great deal with the saturation secondary paper with Marie Gantz as first author.

Comment [mw7]:

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Comment [mw8]: How was this picked. Need to justify. What percentage of infants were classified as ill by this. Eight hours of vent in first 15 days doesn't seem like much!

Comment [AD9]: Perhaps you need a table comparing the analysis sample to the rest of the missed babies to reassure readers that there were no systematically missing data.  
MW Agree.

different study time points, were not significantly different (not shown). The time from birth to initiate feeds and time to achieve full feeds were also similar between groups (TABLE2). The mean 24-hour energy intake on the pre-specified study days was not different between groups and approximated 80kcal/kg/day on day 7, advancing progressively until 36 weeks postmenstrual age, to approximately 100kcal/kg/day. The macronutrient composition of energy source was also not different between groups (TABLE2).

**Comment [AD10]:** I would add a graph over time showing these growth trajectories by group.

**Comment [mw11]:** Agr: graph would be helpful.

**Primary Outcome (TABLE 3):** The rate of the composite primary outcome, weight < 10<sup>th</sup> percentile or death at 36 weeks PMA (or discharge if earlier) did not differ significantly between the lower saturation and the higher saturation groups (55.6 and 57.7% respectively; relative risk with lower oxygen saturation 0.95; 95% confidence interval[CI] 0.8 to 1.1, p = 0.43). Although there was some catch-up growth, and the proportion with growth restriction decreased at the 18-22 months follow-up (35.4 and 31.3%, respectively), the composite outcome of weight < 10<sup>th</sup> percentile or death again was not different between groups (RR 1.1, 95% CI 0.9 to 1.4, p = 0.23).

**Comment [mw12]:** In intro you stated that higher oxygen sat might decrease growth.

Similar results were observed when sub-group analysis was done by gestational age strata.

**Comment [mw13]:** It makes more sense to me to focus on the survivors.

Similarly, the percentage with length and head circumference < 10<sup>th</sup> percentile at 36 weeks PMA was also not different between groups (TABLE4). Again, similarly to the weight outcome, at the 18-22 months follow-up the percentage of infants with length and head circumference < 10<sup>th</sup> percentile was less than that seen at the 36 weeks PMA measure, although the amount of recovery or catch-up was less for length. In-hospital growth velocity was not different between the lower and the higher saturation groups (13.6±2.4 vs. 13.4±2.6 gm/kg/d, p=0.69). The similarity in growth velocity between saturation groups was not influenced by gestational age strata (TABLE 3). The degree of growth restriction at 36 weeks PMA was more pronounced for length (z-score of -2.1) than for weight (-1.5) or head circumference (-1.1).

**Comment [AD14]:** I think this is the first time we see a mention of this composite outcome. You need to justify and mention this outcome at different time points in the Methods section. This also has implications for what your analysis sample (and your denominator) truly is (up until now and looking at fig 1, I was thinking that it was just survivors!).

Similar to the findings in the main trial, the incidence of ROP in this sub-cohort was significantly lower in the lower saturation group (7 vs. 17.8%,  $p=0.0001$ ). The other clinical outcomes, such as death before discharge and BPD (defined as use of supplemental oxygen at 36 weeks PMA), were not different between groups (TABLE 4).

As was intended by the protocol, the median levels of oxygen saturation while on supplemental oxygen differed between randomization groups (FIGURE 2). The number of days on oxygen supplementation was also greater in the higher saturation group. However, as in the main trial, there was a substantial overlap and the actual attained median levels of saturation were higher than the target levels.

When analysis was done by quartiles of the actual attained median saturations, infants with median saturations in the lowest quartile had higher risk for death or weight <10%ile at 36 weeks PMA when compared to the highest quartile (70.3 vs. 43.5%, RR 1.6, 95% CI 1.3-2.0,  $p=0.0001$ ). This was also seen at 18-22 months (51.6 vs. 18.8%, RR 2.6, 95% CI 1.9-3.6,  $p=0.0001$ ) (TABLES). When severity of illness was factored in, an increasing proportion of ill infants were seen when attained SpO<sub>2</sub> decreased from highest to lowest quartile (14, 29, 44 and 51%, respectively;  $p < .0001$ ).

#### Discussion:

In this large, multicenter, trial which randomly assigned, from birth, low gestational age premature infants to lower saturation or higher saturation targets while on supplemental oxygen, we found no difference in the primary outcome of death or weight less than 10<sup>th</sup> percentile (growth restriction) at 36 weeks PMA or at 18-22 months follow-up, by randomized group assignment. We also found no difference in the in-hospital growth velocity between the two groups. However, we did find that when actual attained median oxygen saturations were

**Comment [AD15]:** So how do these results comport with your main findings showing no differences? Would readers be left with a mixed and confusing message?

**Comment [mw16]:** Agree not at all clear what is shown in table and what meaning is of this sentence. This gets circular: you defined illness severity by higher FIO<sub>2</sub> and ventilator: so sicker babies have lower saturations? Isn't that evident?

**Comment [AD17]:** Not clear what you mean; are the rates presented for illness severity or growth outcome?

assessed, infants with median saturations in the lowest quartile had a higher risk for death or weight <10%ile when compared to the highest quartile, both at 36 weeks PMA and 18-22 months corrected age. Our outcomes differ from the observational and non-randomized study of Tin *et al*, who used two different saturation targets from birth by virtue of differing unit policies<sup>18</sup>, and reported that infants cared for in the unit that maintained infants with higher saturation targets were more likely to have growth restriction at discharge, as well as increased risk for ROP and BPD. Other studies of targeted oxygen saturation have not found a difference in growth. Although saturation targeting in the BOOST trial<sup>16</sup> was started at 32 weeks PMA for infants still requiring oxygen supplementation, Askie *et al* found no difference in growth at 36 weeks PMA or at 12 months corrected age. Just recently, the similarly designed Canadian Oxygen Trial reported no difference in percentiles of all parameters of growth at 18 months follow-up<sup>24</sup>. The growth outcome from a meta-analysis of trials that randomize to differing saturations from birth is forthcoming<sup>25,26</sup>.

Consistent with other masked, randomized trials of targeting different oxygen saturation ranges<sup>16,17</sup>, the actual attained oxygen saturation levels have a tendency to overlap, presumably because of the dynamism of preterm infant oxygenation. The frequent episodes of desaturations in the majority of preterm infants require adjustments of the fraction of inspired oxygen (FiO<sub>2</sub>), and lead to wide fluctuations in SpO<sub>2</sub><sup>27</sup>. In the absence of an automated FiO<sub>2</sub> delivery system, or at least one-to-one dedicated nursing, underestimating or overestimating FiO<sub>2</sub> delivery to keep infants tightly within target saturation ranges is difficult<sup>28,29</sup>. Anticipating this limitation, comparison of the extreme quartiles of attained median oxygen saturations shows that spending more time in the lowest quartile (median saturation between 69-91%) is associated with increased risk for death or growth failure. Analysis of severity of illness (defined as FiO<sub>2</sub> > 0.4

Comment [mw18]: Still not following the rationale here. Needs to be more clear.

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and mechanical ventilation for more than 8 hours in the first 15 days) according to quartile of actual median SpO<sub>2</sub>, showed that an increasing proportion of ill infants are seen with decreasing quartiles of attained SpO<sub>2</sub>. However, this may just be another indicator of increased disease severity.

Bronchopulmonary dysplasia is promoted by exposure to oxygen and mechanical ventilation, both variables that infants assigned to the higher saturation group were exposed to for longer periods. Unlike the main trial<sup>19</sup>, wherein the rate of BPD (as defined by use of supplemental oxygen at 36 weeks PMA) was higher in the infants in the higher oxygen saturation group, the difference in the rates for BPD using any definition (moderate or severe by consensus definition or by physiologic definition) did not reach significance in this subgroup. It has been described that preterm infants with morbidities such as BPD have poorer growth<sup>30</sup>. STOP-ROP and BOOST were trials that randomized infants to different saturation targets. Whilst starting a few weeks after birth, they both showed higher rates of pulmonary sequelae and/or BPD in the higher saturation group of infants but growth outcomes were unaffected<sup>16, 17</sup>. Our data does not help to resolve the question of whether the presence of BPD itself promotes the development of growth failure.

**Comment [mw19]:** Likely a power issue – need to mention, subanalysis was not powered for this.

Retinopathy of prematurity is another preterm infant morbidity that is associated with exposure to higher levels of oxygenation. The main trial indeed showed a substantial decrease in severe ROP in survivors who were kept in the lower target saturation range<sup>19</sup>. It has been noted that slow patterns of early weight gain can predict ROP in high risk infants<sup>31, 32</sup>. Insulin-like growth factor-1 (IGF-1) levels are described to be deficient at preterm birth and further reduced by conditions that preterm infants experience (e.g. poor nutrition, acidosis, and sepsis). This deficiency of IGF-1 has been associated with less vessel growth, greater retinal hypoxia and

elevation of hypoxia-induced vasoproliferative factors (e.g. vascular endothelial growth factor) and more severe ROP<sup>33</sup>. In the present study, despite the difference in severe ROP between groups, a ~~similar~~ difference in growth velocities or weight was not seen at any of the time points studied.

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This subgroup of the SUPPORT trial also showed the previously reported increase (although not significant) in mortality in the lower saturation group. When analysis was done by quartiles of the actually attained median oxygen saturation, irrespective of assignment group, there was a higher risk for death in the lowermost quartile when compared to the uppermost quartile. We speculate that the infants whose actual median saturations were in the lower quartiles were more ill and therefore experiencing more episodes of desaturation<sup>34</sup>.

Comment [mw20]: Again power issue

Intermittent determinations of 24-hour nutritional intake ('snapshots') showed that the caloric intake and intake composition was similar between the lower and the higher saturation groups. However, the entire population suffered from sub-optimal intake. Although the earliest time point for collection of nutritional information was age 7 days, the protein intake at this time only translated into about 3.2 grams/kg/d in either group. The importance of improved early protein intake and the association with better growth outcomes is achieving greater recognition<sup>7</sup>. The generally recommended energy intake for healthy low birth weight infants of 90-120 kcal/kg/d<sup>35</sup> was only marginally achieved, even by 36 weeks PMA. Calorie distribution according to macronutrient composition varied over time, but swung from predominantly lipid to predominantly carbohydrate over time; on day 7, there was a predominance of calories from lipid intake (47% lipid, 38% carbohydrate, 15% protein) and by 36 weeks PMA, there was a predominance of calories from the carbohydrate fraction (55% carbohydrate, 35% lipid, 10% protein). This macronutrient distribution is very different from the nutrient supplies that

Comment [mw21]: And has been previously reported from the NRN by Ehrenkrantz.

normally growing fetuses receive (high fraction of amino acids with just enough lipid and glucose)<sup>36</sup>. While some of the limitations to intake relate directly to a baby's clinical condition, it has been shown that the clinician's perception of illness may still limit provision of optimal nutritional intakes<sup>37</sup>. The shortfall in nutritional intake can translate into profound cumulative nutritional intake deficits that may account for the significant rates of growth restriction in this population (46-50%). The rate of growth restriction in the present study appears to be less when compared to older studies, but caution is needed in interpretation as the reference growth curves used in this study under-estimate measures as compared to the older utilized growth curves<sup>21</sup>. The updated intrauterine growth curves represent a contemporary, large, racially diverse US cohort. Compared to the older widely-used, Lubchenco growth curves, these curves are slightly shifted rightward especially at the higher gestational ages. The use of fetal growth reference standards as the ideal for postnatal growth may be another limitation of this study. *In utero* conditions for the fetus are completely different to the extra-uterine environment and the metabolic demands on an infant born prematurely. Comparison between the growth of an infant born preterm and a fetus of the same gestational age places the preterm infant at a great disadvantage, hence the inevitable "excessive" incidence of postnatal growth restriction. Plotting the actual post-natal growth measures of a recent cohort of VLBW infants (including early physiologic weight loss) against fetal growth curves showed that they were consistently below the 10%ile by 36 weeks or discharge<sup>30</sup>.

The strength of our data lie in the large group of preterm infants studied and randomized from birth to two target saturation ranges within the accepted limits at the time. Although the nutritional dataset is limited and we are unable to measure cumulative deficits, the intermittent

measures of nutritional intake demonstrate the consistently inadequate provision of protein and non-protein caloric intakes.

Conclusion:

Oxygen saturation targeting from birth had no impact on growth outcomes, by group. However, when evaluated against actually attained values, the greatest degree of growth restriction was seen in babies with the lowest attained median oxygen saturation levels. The high incidence of postnatal growth restriction persists despite use of an updated growth reference standard, and insufficient caloric provision remains an issue.

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Figure 1. Patient Distribution

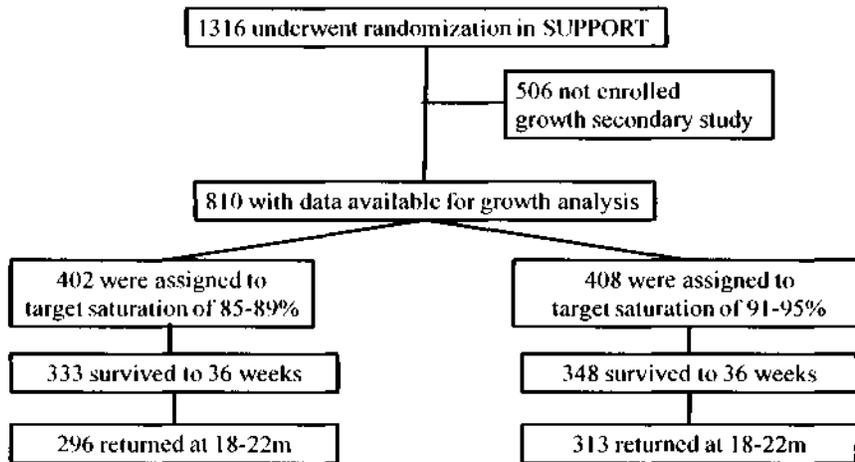


Table 1: Baseline Population characteristics

Characteristic <sup>1</sup>	Lower Saturation n=402	Higher Saturation n=408	p-value <sup>2</sup>
Gestational age, weeks	26.2 (1.1)	26.2 (1.1)	0.65
Birth weight, g.	838.6 (186)	839.9 (191)	0.87
Birth weight < 10 <sup>th</sup> %ile <sup>3</sup> (SGA)	40/402 (10.0)	53/408 (13.0)	0.19
HC at birth	23.5 (1.8)	23.6 (1.9)	0.74
HC at birth < 10 <sup>th</sup> %ile <sup>3</sup>	41/396 (10.4)	53/398 (13.3)	0.19
Length at birth	33.4 (2.9)	33.3 (2.9)	0.22
Length at birth < 10 <sup>th</sup> %ile <sup>3</sup>	50/396 (12.6)	57/400 (14.3)	0.48
Non-Hispanic black	179/402 (44.5)	159/408 (39.0)	0.10
Multiple birth	90/402 (22.4)	112/408 (27.5)	0.14
Antenatal steroids	390/402 (97.0)	389/407 (95.6)	0.29
Vaginal delivery	138/402 (34.3)	147/408 (36.0)	0.56
Mother's education: HS grad	69/311 (22.2)	90/313 (28.8)	0.07
% Male	211/402 (52.5)	236/408 (57.8)	0.19

<sup>1</sup>presented as mean (SD) for continuous variables, n/N (%) Yes for categorical variables.

<sup>2</sup>adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables and robust Poisson regression for categorical variables, where appropriate

<sup>3</sup>based on 10<sup>th</sup> percentile weight for GA, by gender, from Olsen growth tables.

Table 2. Nutritional Intake

Combined parenteral and enteral intake (Kcal/kg/day):	Lower Saturation n=402	Higher Saturation n=408	p-value <sup>2</sup>
<b>Total energy:</b>			
Day 7	84.2 (25.0)	81.8 (22.4)	0.24
Day 14	91.8 (26.1)	90.3 (24.9)	0.57
Day 21	93.8 (37.8)	92.8 (27.54)	0.72
Day 28	97.2 (29.1)	95.6 (29.3)	0.62
32 weeks PMA	104.3 (29.8)	105.2 (27.3)	0.90
36 weeks PMA	110.5(36.4)	108.1 (33.5)	0.47
Discharge or 36 weeks PMA	106.4 (40.5)	100.8 (34.0)	0.83
<b>Protein:</b>			
Day 7	13.2 (3.2)	13.0 (3.3)	0.66
Day 14	12.5 (4.8)	12.1 (4.8)	0.46
Day 21	10.7 (5.3)	10.9 (5.0)	0.60
Day 28	9.9 (5.0)	10.4 (4.9)	0.31
32 weeks PMA	10.0 (5.3)	9.9 (4.9)	0.80
36 weeks PMA	10.5 (5.0)	10.4 (4.9)	0.96
Discharge or 36 weeks PMA	10.7 (5.3)	10.1 (4.3)	0.72
<b>Lipid:</b>			
Day 7	40.4 (14.2)	39.0 (11.8)	0.24
Day 14	39.3 (14.7)	38.7 (12.2)	0.47
Day 21	38.7 (16.5)	38.3 (12.5)	0.48
Day 28	38.8 (12.9)	37.6 (12.2)	0.18
32 weeks PMA	37.8 (12.0)	38.4 (11.5)	0.83
36 weeks PMA	38.4 (11.9)	37.8 (11.9)	0.62
Discharge or 36 weeks PMA	37.3 (12.8)	34.3 (10.8)	0.67
<b>Carbohydrate:</b>			
Day 7	32.9 (15.8)	31.3 (15.3)	0.24
Day 14	43.8 (20.2)	43.5 (20.7)	0.98
Day 21	50.2 (27.0)	49.4 (22.2)	0.93
Day 28	53.7 (22.9)	52.0 (21.9)	0.53
32 weeks PMA	59.1 (20.3)	57.9 (20.3)	0.66
36 weeks PMA	60.8 (20.4)	60.1 (19.9)	0.83
Discharge or 36 weeks PMA	65.8 (23.3)	58.3 (19.4)	0.63
Age at first enteral feed (days) n, median, IQR	373, 4 (3-7)	380, 4 (3-7.5)	0.38
Age at first full enteral feed (days) n, median, IQR	337, 23(16-34)	345, 24 (16-34)	0.76

<sup>1</sup>presented as mean (SD) for continuous variables, except where noted.

<sup>2</sup>adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables; unadjusted rank sum test for age at first enteral feed and age at first full enteral feed

Table 3: Primary Outcomes

Outcome <sup>1</sup>	Lower Saturation N=402	Higher Saturation N=408	p- value <sup>2</sup>
<b>All infants</b>			
<b>36 weeks PMA<sup>3</sup>:</b>			
Death or wt < 10 <sup>th</sup> %ile	223/401 (55.6)	232/402 (57.7)	0.43
Wt < 10 <sup>th</sup> %ile	155/333 (46.6)	172/342 (50.3)	0.30
Growth velocity (g/kg/d) <sup>4</sup>	13.6 (2.4), 260	13.4 (2.6), 275	0.69
<b>18-22 months FU:</b>			
Death or wt < 10 <sup>th</sup> %ile	136/384 (35.4)	122/390 (31.3)	0.22
Wt < 10 <sup>th</sup> %ile	48/296 (16.2)	45/313 (14.4)	0.49
<b>GA 24-25 weeks</b>			
<b>Lower Saturation N=182      Higher Saturation N=174</b>			
<b>36 weeks PMA<sup>3</sup>:</b>			
Death or wt < 10 <sup>th</sup> %ile	122/182 (67.0)	124/172 (72.1)	0.31
Wt < 10 <sup>th</sup> %ile	71/131 (54.2)	85/133 (63.9)	0.17
Growth velocity (g/kg/d) <sup>4</sup>	13.9 (2.1), 98	13.1 (2.8), 110	0.29
<b>18-22 months FU:</b>			
Death or wt < 10 <sup>th</sup> %ile	87/175 (49.7)	78/170 (45.9)	0.55
Wt < 10 <sup>th</sup> %ile	24/112 (21.4)	29/121 (24.0)	0.48
<b>GA 26-27 weeks</b>			
<b>Lower Saturation N=220      Higher Saturation N=234</b>			
<b>36 weeks PMA<sup>3</sup>:</b>			
Death or wt < 10 <sup>th</sup> %ile	101/219 (46.1)	108/280 (47.0)	0.65
Wt < 10 <sup>th</sup> %ile	84/202 (41.6)	87/209 (41.6)	0.76
Growth velocity (g/kg/d) <sup>4</sup>	13.4 (2.6), 162	13.6 (2.5), 165	0.55
<b>18-22 months FU:</b>			
Death or wt < 10 <sup>th</sup> %ile	49/209 (23.4)	44/220 (20.0)	0.30
Wt < 10 <sup>th</sup> %ile	24/184 (13.0)	16/192 (8.3)	0.12

<sup>1</sup> presented as n/N (%). Yes: 36 week outcomes based on Olsen growth tables; follow-up outcomes based on WHO growth tables<sup>2</sup>.

<sup>2</sup> p-values are from robust Poisson regression models and linear mixed models (growth velocity); adjusted for multiple birth clustering, SUPPORT stratification variables center, and gestational age group (models for 'All infants') and multiple birth clustering and center (models for GA subgroups);

\*\*indicates statistical significance (p<.05)

<sup>3</sup> include infants discharged prior to 36 weeks PMA.

<sup>4</sup> calculated for the subset of survivors to 36 weeks PMA or discharge/transfer, whichever came first using the exponential method (Patel 2005, 2009) with available growth study data at Day 1 & 36 weeks ; presented as mean (SD), n.

Table 4. Clinical and other Anthropometric Outcomes

Characteristic <sup>1</sup>	Lower Saturation n=402	Higher Saturation n=408	p-value <sup>2</sup>
Death by 36 weeks PMA	69 (17.2)	60 (14.7)	0.39
BPD, oxygen at 36 weeks PMA	132/333 (39.6)	158/348 (45.4)	0.08
Postnatal steroids for BPD	33/394 (8.4)	39/399 (9.8)	0.39
# days on ventilator <sup>3</sup> , n, median, mean(SD)	n=329 9,21.0 (25.6)	n=344 14.5,22.7 (24.7)	0.17
# days supplemental oxygen <sup>3</sup> , n, median, mean(SD)	n=329 47,53.1 (37.6)	n=344 60,60.6 (36.6)	0.0094**
Median SpO2 while on supp. oxygen, n, median (IQR)	382, 92 (91 to 94)	389, 94 (93 to 95)	<.0001**
Severe IVH	58/391 (14.8)	60/396 (15.2)	0.85
PVL	16/392 (4.1)	20/397 (5.0)	0.57
NEC	51/397 (12.9)	48/404 (11.9)	0.65
Late onset sepsis	144/397 (36.3)	139/404 (34.4)	0.70
PDA	181/397 (45.6)	200/403 (49.6)	0.27
Severe ROP	21/302 (7%)	56/314 (17.8%)	.0001**
n /N(%) with L <10th %ile at 36wk PMA	203/314 (64.7)	218/315 (69.2)	0.21
n /N(%) with L <10th ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n /N(%) with HC <10th %ile at 36wk PMA	124/319 (38.9)	130/325 (40.0)	0.87
n /N(%) with HC <10th ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

<sup>1</sup>presented as mean (SD) for continuous variables, n/N (%) Yes for categorical variables, except where noted.

<sup>2</sup>adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center, using linear mixed models for continuous variables and robust Poisson regression for categorical variables, where appropriate; unadjusted rank sum test for days on ventilator and median SpO2

\*\*indicates statistical significance (p<.05)

<sup>3</sup>subset of survivors to discharge, transfer, or 120 days, whichever came first

Figure 2. Distribution of Actual Median Saturation while on Supplemental Oxygen

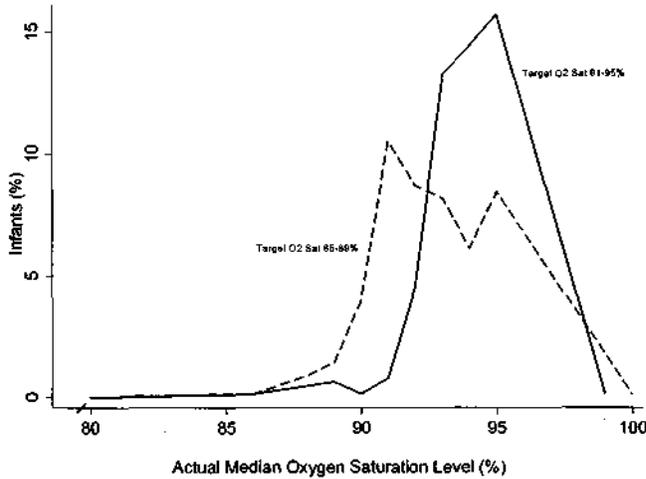


Table 5: Primary outcomes by actual median O2 saturation quartile<sup>1</sup>

Outcome <sup>1</sup>	Quartile 1 n=158	Quartile 2 n=267	Quartile 3 n=158	Quartile 4 n=188	RR Q1 vs. Q4 (95% CI)	p-value <sup>2</sup>
<b>36 weeks PMA<sup>3</sup>:</b>						
Death	52/158 (32.9)	37/267 (13.9)	16/158 (10.1)	12/188 (6.4)	5.0 (2.8-8.9)	<.0001**
Death or wt < 10 <sup>th</sup> %ile	111/158 (70.3)	162/267 (60.7)	78/155 (50.3)	81/185 (43.8)	1.6 (1.3-2.0)	<.0001**
Wt < 10 <sup>th</sup> %ile	60/107 (56.1)	125/230 (54.4)	62/139 (44.6)	69/173 (39.9)	1.4 (1.1-1.8)	.0060**
<b>18-22 months FU:</b>						
Death	63/157 (40.1)	52/256 (20.3)	21/146 (14.4)	16/178 (9.0)	4.3 (2.7-7.1)	<.0001**
Death or wt < 10 <sup>th</sup> %ile	81/157 (51.6)	90/256 (35.2)	38/146 (26.0)	32/178 (18.0)	2.7 (2.0-3.8)	<.0001**
Wt < 10 <sup>th</sup> %ile	18/94 (19.2)	38/204 (18.6)	17/125 (13.6)	16/162 (9.9)	1.9 (1.0-3.4)	.0366**

<sup>1</sup> Outcomes presented as n/N(%), and Relative Risk (RR)

<sup>2</sup> adjusted for multiple-birth clustering and SUPPORT stratification variables GA group and center using robust Poisson regression.

\*\* indicates statistical significance (p<.05)

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions  
**Date:** Tuesday, July 23, 2013 1:10:00 PM

---

I assume we will discuss at steering committee?  
Approach?

Michele Walsh  
Chief Division of Neonatology  
Rainbow Babies & Childrens Hospital  
Professor of Pediatrics  
Case Western Reserve University  
11100 Euclid Avenue, Mailstop 6010  
Cleveland, OH 44106-6010  
email: michele.walsh@cwru.edu  
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Fax: (216) 844-3380

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

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Thursday, June 27, 2013 1:06 AM  
To: Bell, Edward (Pediatrics)  
Cc: Wally Carlo; Krisa P Van Meurs (vanmeurs@stanford.edu); Uday Devaskar; Kristi Watterberg; Bill Truog; Kathleen Kennedy; Jon Tyson; Pablo Sanchez; Brenda Poindexter; Seetha Shankaran; Michele Walsh; Leif Nelin; Kurt Schibler; Barbara Stoll; Ron Goldberg; Barbara Schmidt; Abbot Laptook; Carl D'Angio; Abhik Das; Rosemary Higgins  
Subject: Re: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

Thanks Ed  
I think the SUPPORT group should submit recommendations and be represented  
The NRN will no doubt want to also be a part of this  
I will wait to hear how the NRN wants to proceed  
Be well  
Neil

On Jun 26, 2013, at 10:51 AM, "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu> wrote:

> FYI

>

> -----Original Message-----

> From: Office for Human Research Protections (OHRP) [mailto:OHRP-L@list.nih.gov] On Behalf Of Irene Stith-Coleman

> Sent: Wednesday, June 26, 2013 3:21 PM

> To: OHRP-L@list.nih.gov

> Subject: HHS Announces Public Meeting and Request for Comments Regarding Application of Regulatory Requirements to Research Studying Standard of Care Interventions

>

> On June 26, 2013, the Department of Health and Human Services (HHS) announced in the Federal Register an August 28, 2013 public meeting to seek public input and comment on how certain provisions of the Federal policy for the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically requests input regarding how an

institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process.

- >
- > HHS is seeking participation in the meeting and written comments from all interested parties, including, but not limited to, IRB members, IRB staff, institutional officials, research institutions, investigators, research subject advocacy groups, ethicists, and the regulated community at large. The meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects. HHS is seeking input on a number of specific questions but is interested in any other pertinent information participants in the public meeting would like to share.
- >
- > The public meeting will be held on August 28, 2013, from 9 a.m. to 5 p.m., in the Hubert H. Humphrey Building, 200 Independence Ave., SW, Great Hall, Washington, DC 20201; Metro: Federal Center SW station.
- >
- > **Deadline for Registering to Attend the Public Meeting:**
- > While there is no registration fee, individuals planning to attend the public meeting in person must register to attend. Registration to attend the meeting will be accepted on a first-come, first-served basis and must be received no later than 5 p.m. on August 14, 2013. Due to space limitations, the number of registrants will be capped.
- >
- > **Deadline for Registering to Present at the Public Meeting:**
- > Registration to present at the public meeting will be accepted on a first-come, first-served basis and must be received no later than 5 p.m. on August 7, 2013.
- >
- > **Deadline for Submitting Comments for the Public Meeting:**
- > Written comments for discussion at the public meeting must be received no later than 5 p.m. on August 7, 2013.
- > **Deadline for Submitting Comments after the Public Meeting**
- >
- > In addition to materials submitted for discussion at the public meeting, individuals may submit other written comments after the public meeting. These comments must be received no later than 5 p.m. on September 9, 2013 for consideration by HHS.
- >
- > An alternative to attending the meeting in person will be provided. Participants who cannot attend the public meeting in person will have an option to view it via live streaming technology. Information on that option will be posted at a later time on the OHRP website at <http://www.hhs.gov/ohrp>.
- >
- > The Federal Register notice announcing the public meeting and details about the following: registering to attend, registering to present at the meeting, submitting written comments, viewing the public meeting via live streaming, issues for discussion, special accommodations, and, additional background information, can be accessed at: <http://www.hhs.gov/ohrp/newsroom/rfc/Public%20Meeting%20August%2028,%202013/aug28public.html>
- >
- >
- >
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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Hudson, Kathy (NIH/OD) [E]  
**Sent:** Tuesday, July 23, 2013 10:39 AM  
**To:** Guttmacher, Alan (NIH/NICHD) [E]; White, Pat (NIH/OD) [E]  
**Cc:** Devaney, Stephanie (NIH/OD) [E]  
**Subject:** FW: Final QFR  
**Attachments:** SUPPORT Clinical Trial.docx

This was (b)(5) (It was (b)(5)

(b)(5) The attached revision is being sent to senate to replace old version. It keeps the (b)(5)

(b)(5) which is a triumph.

## **SUPPORT Clinical Trial**

The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.

1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:

OHRP referenced in the articles cited in a letter dated June 4, 2013, from OHRP to the University of Alabama the specific scientific data that existed at the start of the SUPPORT study that OHRP relied on in reaching its conclusion. The letter and article references can be found on OHRP's web site at [http://www.hhs.gov/ohrp/detrm\\_lettrs/YR13/jun13a.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/YR13/jun13a.pdf). NIH subsequently responded in disagreement with the conclusions and stated the more recent data generated with more sophisticated oxygen-monitoring and oxygen-measurement devices showed no increased risk of death or neurological damage (see <http://www.nejm.org/doi/full/10.1056/NEJMp1306986>). OHRP and NIH are continuing to review these considerations. In addition, HHS will hold a public meeting to seek public input and comment on how certain provisions of the HHS requirements related to the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the nonresearch context on August 28, 2013.

2. If no such data existed, could you please explain why it would be scientifically credible or ethical to explain unknown risks of a study?

Response:

Please see response above regarding specific scientific data. HHS does not and has not questioned whether the design of the SUPPPORT study was ethical.

3. What is the process for appealing the findings of OHRP? Is there a mechanism for having an independent review of OHRP actions especially when they are so universally called into question as in this case? (Please see, for example, editorials and correspondence in the New England Journal of Medicine and The Hastings Center Bioethics Forum).

Response:

OHRP's compliance oversight procedures state that an institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation, <http://www.hhs.gov/ohrp/compliance/evaluation/index.html>. OHRP has no recollection of any such requests for reconsideration from an institution against which OHRP made a determination of noncompliance. Historically, OHRP has received such requests only from complainants concerned that OHRP did not agree with their allegations of noncompliance. If such complainants are unsatisfied with

**the response of the OHRP Director, OHRP informs them that they may communicate with the Principal Deputy Assistant Secretary for Health and the Assistant Secretary for Health and ask them to review the matter.**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Kaeser, Lisa (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Willinger, Marian (NIH/NICHD) [E]  
**Subject:** RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)  
**Date:** Monday, July 22, 2013 5:05:00 PM

---

Unfortunately, Valerie and I were not able to speak as she has a (b)(6) Will keep folks posted.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 12:55 PM  
**To:** Kaeser, Lisa (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]  
**Subject:** RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Hi  
Thanks for your help  
I am going to speak with Valerie Bonham later this afternoon.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Kaeser, Lisa (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 11:06 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]  
**Subject:** RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Honestly, this is a semi-legal proceeding. Tiffany works for OMA - -you should probably ask her who else will be in the meeting with you. Who were you working with in OGC, if anyone?

Lisa

*Lisa Kaeser, J.D.*  
*Director, Office of Legislation and Public Policy*  
*Eunice Kennedy Shriver National Institute*  
*of Child Health and Human Development/NIH*  
*31 Center Drive, MSC 2425*  
*Building 31, Room 2A03*  
*Bethesda, MD 20892*  
*301-496-0536*  
*[kaeser@mail.nih.gov](mailto:kaeser@mail.nih.gov)*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 8:55 AM  
**To:** Willinger, Marian (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Kaeser, Lisa (NIH/NICHD) [E]  
**Subject:** FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

FYI –

Is there someone that can let me know how these items are usually handled?

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 8:53 AM  
**To:** Brown, Tiffany (NIH/OD) [E]  
**Subject:** RE: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Hi

I am available:

July 23 – 9 am- 5 PM

July 24 – 9 am – noon

July 26 – 3-5 PM

July 29 – 10:30 am – 5 PM

July 30 – 10 am – 1 pm; 230 pm – 5 PM

Let me know if you need more options

Rose

Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Brown, Tiffany (NIH/OD) [E]  
**Sent:** Monday, July 22, 2013 8:46 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

**DUE DATE:** noon on July 23, 2013  
**ACTION:** Please send your availability to meet with the OIG  
**CONTACT:** Tiffany Brown, OMA, 301.496.2464

Good morning Dr. Higgins,

The OIG is currently conducting a study entitled, "*Office of Human Research*

*Protections Oversight of the SUPPORT Clinical Trial*" (OEI-01-13-00420). This Congressionally requested study will examine the extent to which the Office for Human Research Protections (OHRP) followed procedures and exercised its discretion in its compliance evaluation of the SUPPORT clinical trial (start notice and study design attached).

While meeting with OHRP, it was suggested that the OIG talk with NIH to discuss the questions below. The OIG met with Dr. Kathy Hudson on July 19<sup>th</sup> to discuss these issues and she thought that it would be a good idea that they speak with you.

- When did NIH become aware of OHRP's review of the SUPPORT trial and UAB?
- What was NIH's involvement in OHRP's review?
- Did NIH express any concerns about the informed consent document?
- From NIH's perspective, was the conduct of OHRP's review typical?
  - Why or why not?
- What actions, if any, did NIH's take after OHRP issued the determination letter to UAB?

Please let me know if your availability to meet with the OIG in a one-hour teleconference, which could potentially happen within the next week, or so.

Thanks in advance for your cooperation!

TIFFANY BROWN  
NIH/OD/OMA  
(301) 496-2464 - DIRECT  
(301) 402-0169 - FAX

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** RE: Confidential:FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)  
**Date:** Monday, July 22, 2013 5:03:00 PM

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Valerie

I hope things are ok with (b)(6)

We can reschedule the call - let me know some possible times. As far as I know, I am available

July 23 - open all day

July 24 - open 830 am -1230 pm

July 26 - 3- 5 pm

Take care

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
NIH  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-435-7909  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, July 22, 2013 12:49 PM  
**To:** Bonham, Valerie (NIH/OD) [E]  
**Subject:** RE: Confidential:FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

I can be reached on my cell phone (b)(6) as I am teleworking.

Hope your (b)(6)

Regards

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy  
and Perinatology Branch NIH  
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higginsr@mail.nih.gov

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

From: Bonham, Valerie (NIH/OD) [E]  
Sent: Monday, July 22, 2013 12:47 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Confidential:FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Hi,

Let's do 4 to 5. My (b)(6) What number shall in all?  
Val

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From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Monday, July 22, 2013 9:28 AM  
To: Bonham, Valerie (NIH/OD) [E]  
Subject: Confidential:FW: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

Valerie  
Would you have time for a brief call related to the attachments?  
I am available today from 2-3 and 4-5 – let me know – I am teleworking from home.  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch NIH  
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301-496-5575  
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higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>

From: Brown, Tiffany (NIH/OD) [E]  
Sent: Monday, July 22, 2013 8:46 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: ACTION: Request for availability for a meeting to meet with the OIG on a review entitled, "Office of Human Research Protections Oversight of the SUPPORT Clinical Trial" (OEI-01-13-00420) - (Due by noon on 7/23/13)

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