Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. All Study End Points

The primary endpoint for this study was both an efficacy and safety endpoint. Improved death and BPD rates suggest efficacy, while worse rates suggest a safety problem. As such, all comparisons are inherently two-sided. Interim and final analyses present the classic spectrum of decisions: superiority, non-inferiority, and inferiority.

Primary Efficacy Endpoint

To compare the rate of Death or BPD between the two intervention arms, with BPD being defined using a standardized oxygen reduction test. The primary endpoint will be recorded at 36 weeks PMA.

Secondary Efficacy Endpoints

The pre-specified secondary efficacy endpoints are defined below. The timing of evaluation of each endpoint is given in bolded font.

Delivery Room (DR):

1. Heart rate in the DR
   Categorical variable with 3 levels: <60, 60-100, >100
2. Type of respiratory support (CPAP, PPV) on departure from DR
3. Fraction of Inspired Oxygen (FiO_2) on departure from DR
4. Pressure-volume characteristics in the DR (at several but not all sites)
5. Need for intubation in DR

First 48 hours of life:

6. Use of inotropes
   Any use within first 48 hours of life
7. Pneumothorax
   Source documentation needed for adjudicated yes/no variable
8. Need for new chest drains
   Calculated as an increase in the number of chest drains recorded hourly.
9. Oxygen requirement of $FiO_2 \geq 40\%$ for 2 hours or more
10. Highest FiO_2 level recorded during the first 48 hours post DR
11. Area under the hourly FiO_2 curve
12. Need for intubation in DR or during first 48 hours of life

First 7 days of life:

13. Death or need for positive pressure ventilation at 7 days

First 10 days of life:

14. Need for new chest drains
    Calculated as an increase in the number of chest drains recorded hourly for the first 48 hours, and then daily up to 10 days of life.
15. Duration of any chest drain
    Calculated as the amount of time the number of chest drains is >0. Since this will be measured hourly for 48 hours and then daily, the finest level possible will be calculated for each infant and then the data will be examined to determine the scale for analysis.
16. Highest FiO_2 level recorded from 48 hours to 10 days of life
17. Air leak
    Defined as radiographic evidence of pneumothorax, pulmonary interstitial emphysema (PIE) or pneumopericardium.

36 weeks PMA:

18. Death
19. BPD defined using a standardized oxygen reduction test

Discharge:

20. Retinopathy of prematurity (ROP) stage 3 or greater requiring treatment
21. Death in hospital
22. Survival to discharge home without BPD, retinopathy of prematurity (grades 3 & 4), or significant brain abnormalities on head ultrasound
23. Length of hospital stay in days
24. Use of postnatal steroids for treatment of BPD
25. Duration of respiratory support (ventilation, CPAP, supplemental oxygen) in days

22-26 Months corrected gestational age:

26. Neurodevelopmental outcomes
27. Respiratory outcomes

Safety

The primary safety endpoint was:

Death or BPD at 36 weeks PMA.

The pre-specified secondary safety endpoints were:

1. Death within 48 hours of delivery.
2. Oxygen requirement of $FiO_2 \geq 40\%$ for 2 hours or more within the first 48 hours post delivery.
3. Rate of pneumothorax within the first 10 days of life.
4. Rate of pulmonary interstitial emphysema (PIE) within the first 10 days of life.
5. Rate of pneumopericardium within the first 10 days of life.
    - Items 3-5 were determined by radiographic evidence and supplemented by data on a) any chest tube in-situ post DR and b) need for new chest tube after arrival in NICU.
6. Grade 3 or 4 IVH within the first 10 days of life. Head ultrasound findings will be used to determine incidence of IVH.
7. Any other serious adverse events that have been adjudicated as potentially relating to the intervention

Pre-specified Adverse Events

The DSMC reviewed all safety outcomes listed above as serious adverse events. In addition, the following pre-specified adverse events were also requested and reviewed:

Serious Adverse Events:

1. Epinephrine in the first 48 hours
2. Chest compressions in the first 48 hours

Adverse Events:

3. Grade 1 or 2 IVH within the first 10 days of life.
4. Infant requiring > 30% Oxygen or NC > 2 LPM on day of life 28.
5. Infant on mechanical support (includes CPAP, NIPPV, invasive ventilation via ETT) on day of life 28.

eMethods 2. Methods of the Post Hoc Bayesian Futility Analysis

The Bayesian interim analysis did not control the conclusions of the DSMC. That decision, made in the presence of the unblinded statistician, was based on safety considerations that occurred only after case by case review by the DSMC clinicians on the possible association of reported adverse events and the timing of those events related to birth. For that reason, we have not given much detail in the manuscript.

The post hoc Bayesian analysis was designed and implemented by the "unblinded" statistician (ARL) in response to an initial DSMC meeting in which the DSMC members became concerned about the potential for futility when the planned interim analysis suggested that the outcomes might be somewhat worse in the intervention patients. This analysis was not preplanned at the start of the study, but rather was meant to inform the deliberations of the DSMB when the members became concerned about safety.

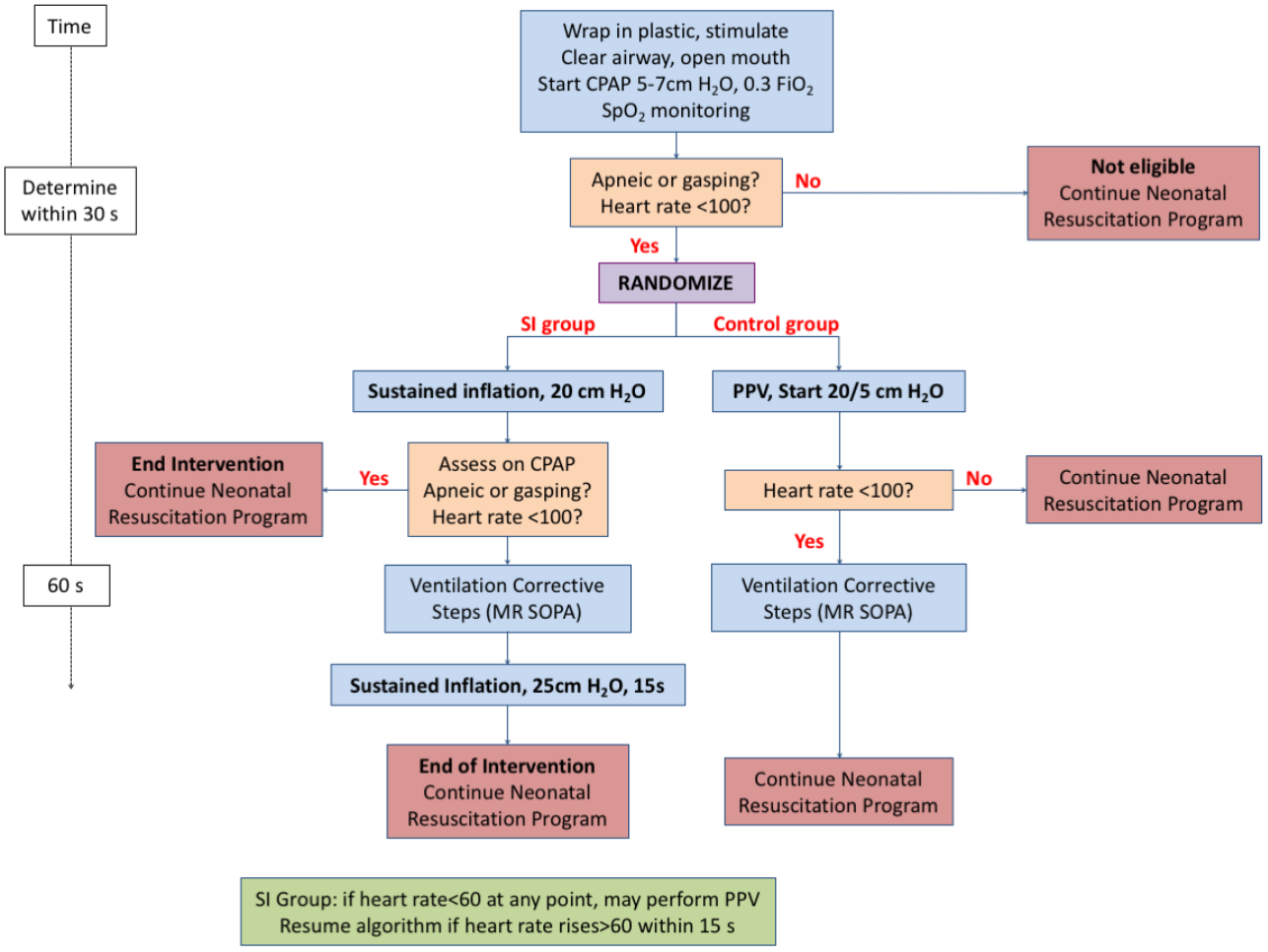
The Bayesian analysis followed the guidance and advice of Saville and colleagues (2014) because of the ability of a Bayesian approach to estimate predicted probabilities of achieving significant results in favor or either treatment arm or of finding indeterminate results. ***(****Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. Clin Trials. 2014; 11(4):485-93. [PMID: 24872363])*

We implemented this approach using software designed precisely for this purpose from MD Anderson Cancer Center (Wathen 2014). The particular implementation of a Bayesian interim analysis was controlled by the requirements of the software of Wathen and colleagues. This software is published and well documented. (*23. Wathen K, et al. Predictive Probabilities User's Guide Version 1.5. March 19, 2014 https://biostatistics.mdanderson.org/softwaredownload/ProductSupportFiles/PredictiveProbabilit/PredictiveProbabilitiesUsersGuide.pdf Accessed 12/28/2017*)

In brief, we used the interim results from the current study as of the time of the final DSMC meeting (Jan 2018) together with prior estimates of risk of adverse outcomes in each of the treatment arms, and the planned number of patients to be enrolled in each arm (n=300 per arm) as of the conclusion of the study. Prior probability estimates took the form of specifying hypothetical data on the mortality risk of each treatment. The larger the number of hypothetical patients in this hypothetical prior study, the greater the amount of information available for a prior probability of study outcomes. We also varied the event rate (mortality) in the two treatment arms to correspond to non informative priors (equal mortality in the two arms) and informative prior probabilities (different event rates per arm).

Using the approach and software described previously, we assessed the alternatives listed in Table 1. This was the table presented to the DSMC in closed session. It includes the prior probability death rates and the prior sample size, as described previously, and then the probabilities of outcomes at the end of the study for results that would favor either arm or neither arm (indeterminate). An indeterminate result was one that would favor neither treatment arm.

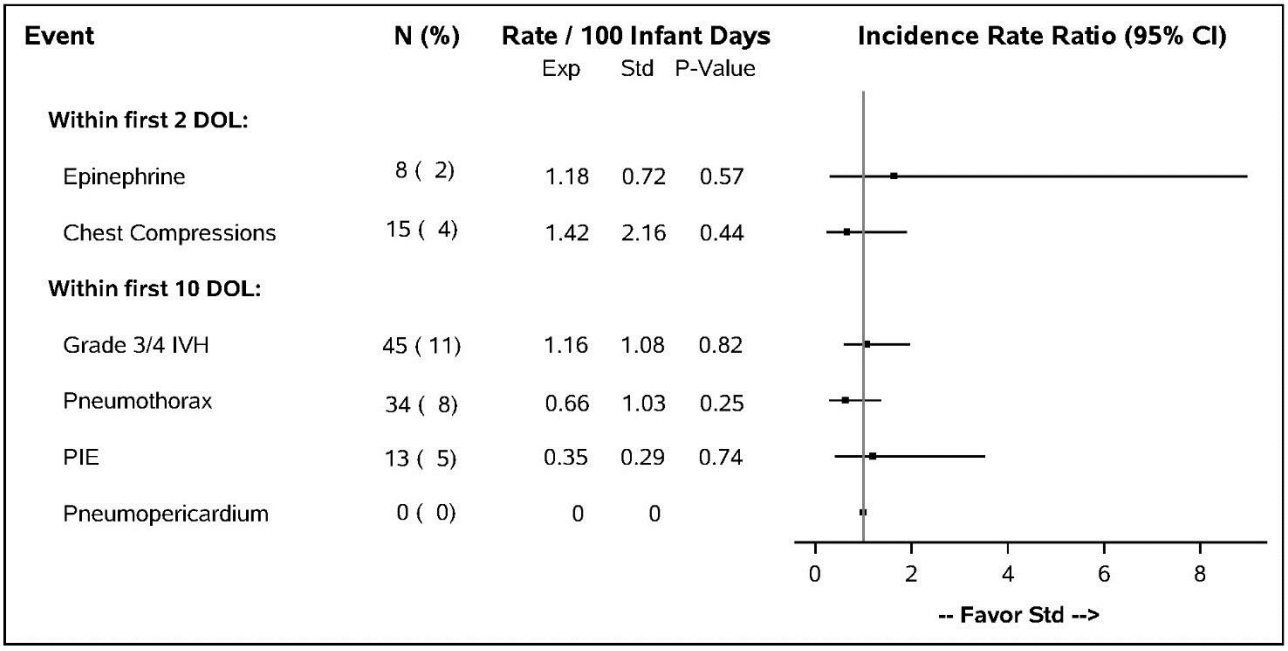
eFigure 1. Assessment of Eligibility, Randomization, and Delivery of Sustained Inflation



Legend eFigure 1: (Modified from Reference 12. Foglia EE, Owen LS, Thio M, Ratcliffe SJ, Lista G, Te Pas A, Hummler H, Nadkarni V, Ades A, Posencheg M, Keszler M, Davis P, Kirpalani H. Sustained Aeration of Infant Lungs (SAIL) trial: study protocol for a randomized controlled trial. Trials. 2015 15;16:95

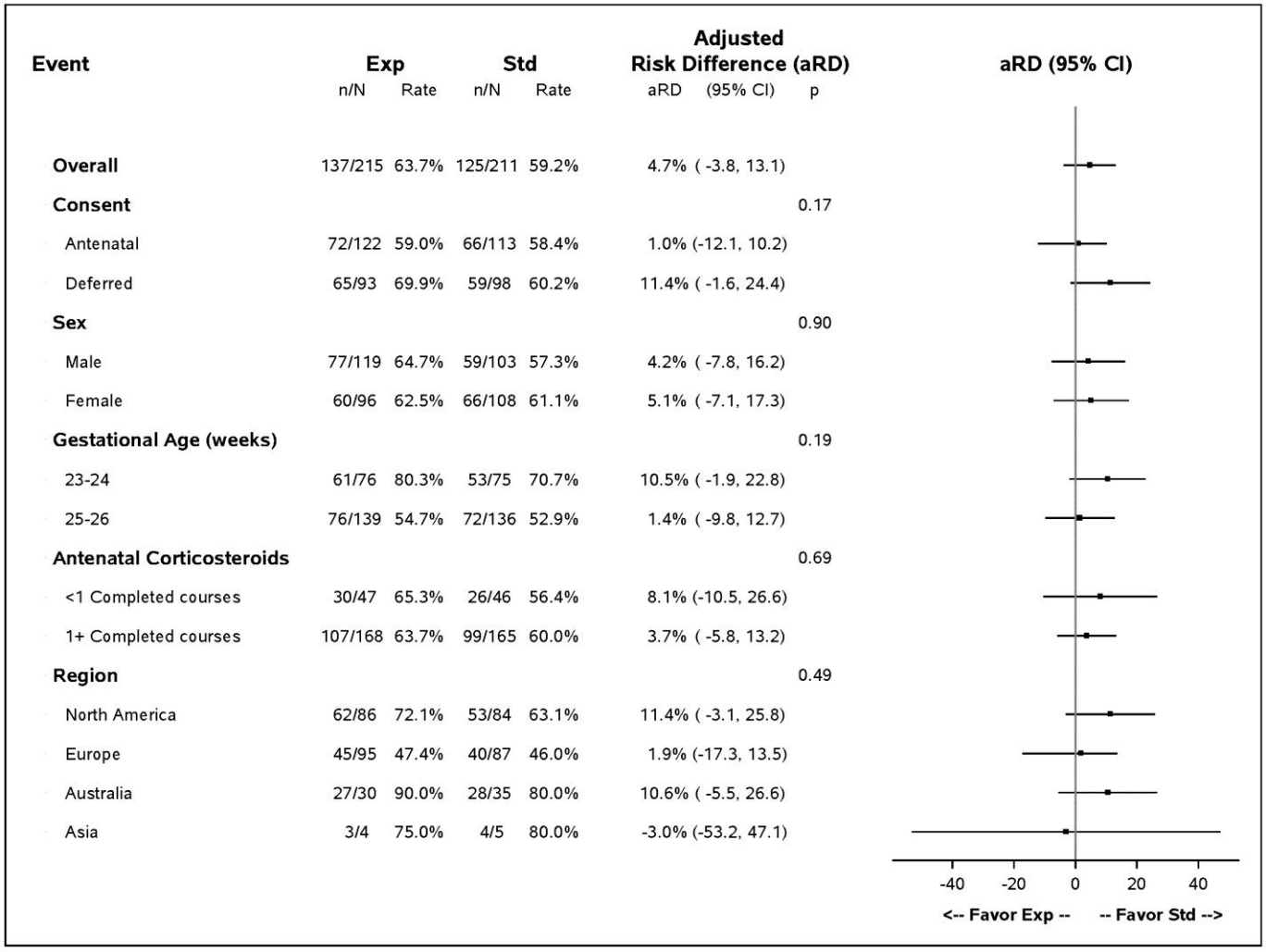
The infant was handled at delivery according to standard guidelines[10-11,14-15], including thermal care, mild stimulation, clearing of airways. If following this the infant was apneic or gasping or if the heart rate was <100 bpm, the infant was eligible for randomization. In addition, providers could initiate positive pressure ventilation if the heart rate fell <60 bpm at any point in the intervention resuscitation algorithm – again in compliance with guidelines [10-11,14-15].

eFigure 2. Incidence Rates of Prespecified Secondary Safety Outcomes and Adverse Events, Accounting for Days at Risk



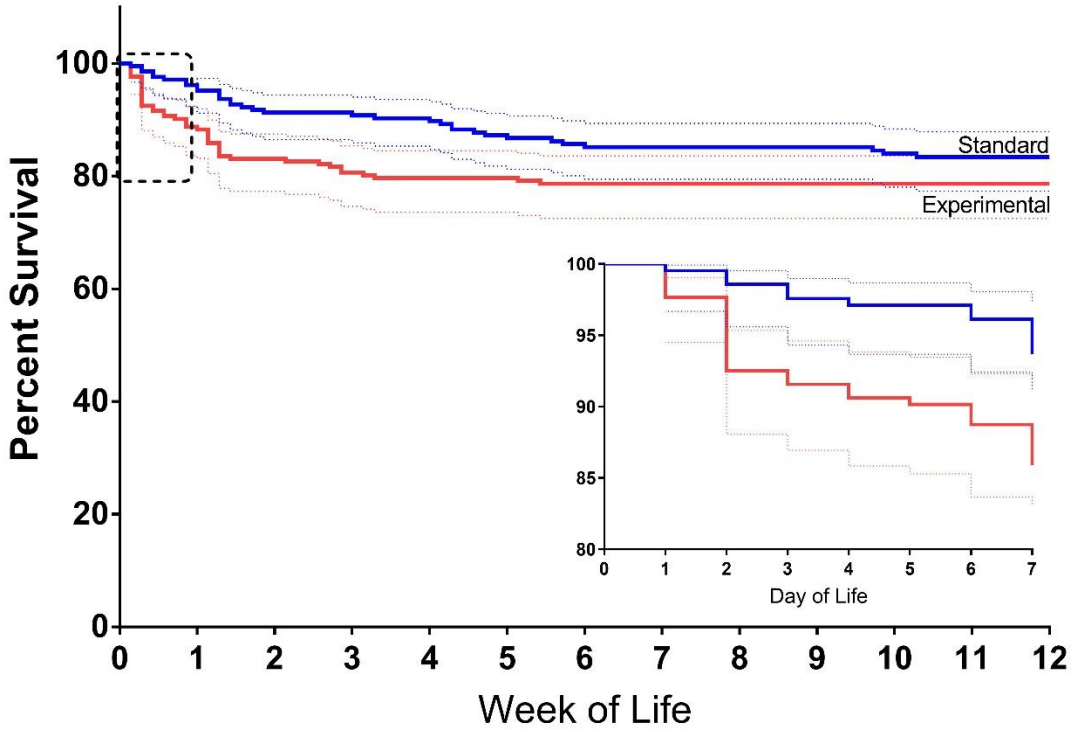
Legend eFigure 2: These pre-specified markers of harm, were chosen *a priori* by the executive committee and the DSMC together. The experimental resuscitation rates are indicated by “Exp”, the standard resuscitation rates by “Std”. To account for days at risk, eFigure 2 shows events, expressed as a function of the rate/per 100 infant days (as Incidence Rate Ratios) to enable events to be equitable across survival time. GEE based Poisson regression was used to compute incidence rate ratios and p-values.

eFigure 3. Primary Outcome and Interaction by Subgroup



Legend eFigure 3: The experimental resuscitation rates are indicated by “Exp”, the standard resuscitation rates by “Std”. The figure displays the risk difference as calculated from a GEE model, adjusted for correlation between multiple births. Covariates adjusted for were gestational age, site, infant sex, maternal corticosteroid use, initial heart rate, small for gestational age, and consent type used. The p-values shown are tests of interactions between the intervention and the subgroup.

eFigure 4. Post Hoc Kaplan-Meier Survival Curves by Group



Number at Risk

Week of Life	0	1	2	3	4	5	6	7	8	9	10	11	12
Experimental	215	188	177	168	164	159	156	154	145	143	134	124	110
Standard	211	197	187	185	181	171	162	158	152	149	140	130	120

Legend eFigure 4: Post-Hoc Kaplan-Meier survival curves, and 95% confidence intervals, by group. Survival curves are shown over the first 12 weeks of life and by day of life within the first week of life. Percent survival (solid lines) and 95% CI (dotted lines) for the group arm is in blue; SI group in red. The insert is an expanded view of the first 7 days of life, showing that the early mortality continued to accrue until day 7. In the larger scale, it can be seen that this mortality does not increase further. Log-rank test of the first 7 days of life showed a statistically significant difference between arms (p=0.001) while the entire first 12 weeks of life showed no difference (p=0.11).

eTable 1. Adjusted Comparisons of Exploratory Secondary Outcomes by Group

Outcome - No. (%)	Experimental Resuscitation (n=215)	Standard Resuscitation (n=211)	Adjusted Risk Difference[1], % (95% CI)	p-value[2]
Delivery Room:				
Surfactant Administered in delivery room	107 (49.8)	105 (49.8)	1.3 (-7.1, 9.8)	0.76
Epinephrine Administered in delivery room	6 (2.8)	3 (1.4)	1.3 (-1.5, 4.0)	0.37
Chest Compressions in delivery room	7 (3.3)	13 (6.2)	-3.7 (-7.8, 0.4)	0.78
First 10 Days of Life:				
Total surfactant doses over first 10 days of life				0.85
0	62 (28.8)	65 (30.8)		
1	103 (47.9)	96 (45.5)		
2	42 (19.5)	45 (21.3)		
3+	8 (3.8)	5 (2.4)		
Hospital Discharge:				
Retinopathy of prematurity (any grade)*	99/196 (50.5)	97/182 (53.3)	-3.9 (-13.8, 6.0)	0.45
Necrotizing Enterocolitis*	21/196 (10.7)	32/186 (17.2)	-6.3 (-13.3, 0.8)	0.08
IVH (any grade)	65 (30.2)	61 (28.9)	1.5 (-7.5, 10.4)	0.75
Pulmonary Hemorrhage*	12/196 (6.1)	18/186 (9.7)	-3.6 (-8.9, 1.7)	0.18
Patent Ductus Arteriosus requiring therapy*	106/196 (54.1)	114/186 (61.3)	-6.3 (-15.5, 2.9)	0.18
Ventilation on DOL 3* [3]	92/182 (50.5)	96/186 (51.6)	1.0 (-8.3, 10.3)	0.84
Ventilation on DOL 7* [3]	80/171 (46.8)	90/182 (49.5)	-1.7 (-10.7, 7.3)	0.72
Ventilation on DOL 14* [3]	74/160 (46.3)	82/169 (48.5)	-0.9 (-10.0, 8.3)	0.85
Ventilation at 36 weeks* [3]	11/169 (6.5)	7/171 (4.1)	2.4 (-2.5, 7.3)	0.34

[1] Risk difference of (experimental - standard resuscitation) calculated using marginal probabilities from adjusted GEE models.
[2] p value calculated from adjusted GEE models. Since no outcome reached statistical significance, p-values are not adjusted for multiple outcomes.
[3] Duration of ventilation was not assessed on a continuous basis but only at discrete time points.
* Outcome with missing data due to transfer or death prior to assessment. Both the number of infants with the outcome and the number assessed are shown.
CI = confidence interval; IVH = Intraventricular hemorrhage

Legend eTable1: Results expressed as Risk Differences (95% CI), calculated using marginal probabilities from the adjusted GEE models. Covariates adjusted for were gestational age, site, infant sex, maternal corticosteroid use, initial heart rate, small for gestational age, and consent type used. Also adjusted for the correlation between infants from multiple births.

eTable 2. Sensitivity Analysis for Primary Outcome and Components Using Only Oxygen Reduction Test Ascertained Component

Outcome; No. (%)	Experimental Resuscitation (N=213)	Standard Resuscitation (N=202)	Adjusted Risk Difference[1] (95% CI)	Adjusted Relative Risk (95% CI)	p value[2]
Death or BPD	136 (63.8)	117 (57.9)	6.43% (-2.08, 14.94)	1.11 (0.96, 1.28)	0.14
Death	45 (21.1)	33 (16.3)	4.89% (-2.77, 12.54)	1.27 (0.87, 1.85)	0.21
BPD	91 (42.7)	84 (41.6)	2.70% (-6.26, 11.66)	1.06 (0.86, 1.31)	0.55

[1] Risk difference of (experimental - standard resuscitation) calculated using marginal probabilities from adjusted generalized estimating equation (GEE) models. Covariates adjusted for were gestational age, site, infant sex, maternal corticosteroid use, initial heart rate, small for gestational age, and consent type used. Also adjusted for the correlation between infants from multiple births.

[2] p value from comparison of adjusted risk difference

Note: BPD = Bronchopulmonary dysplasia

Legend eTable2: The primary intention to treat analysis was performed, using all available methods to diagnose BPD. If only the ORT was used for this, 11 infants were excluded. eTable 2 shows that when these are excluded, there is no effect upon the primary outcome or the component of BPD.

eTable 3. Characteristics of Three Groups of Infants: Early Death, Late Death (to 36 Weeks' Gestational Age), and Survival at 36 Weeks' Gestational Age

Characteristic; No. (%)	Early Death (<48 hours age) (n=19)	Late Death (By 36 weeks) (n=59)	Alive at 36 wks (n=348)
Consent Type			
Antenatal	10 (52.6)	30 (50.8)	195 (56.0)
Deferred	9 (47.4)	29 (49.2)	153 (44.0)
Maternal Age (years); median (IQR)	33.8 (26.9, 37.0)	31.1 (27.4, 34.5)	30.6 (26.0, 35.1)
Maternal Race			
White	12 (63.2)	38 (64.4)	208 (59.8)
Black	2 (10.5)	7 (11.9)	70 (20.1)
Asian	3 (15.8)	9 (15.3)	29 (8.3)
Other[1]	2 (10.5)	5 (8.5)	41 (11.8)
Receipt of antenatal corticosteroids:			
Any	17 (89.5)	55 (93.2)	341 (98.0)
Full course	13 (68.4)	40 (67.8)	280 (80.5)
Placental abruption	7 (36.8)	8 (13.6)	46 (13.2)
Chorioamnionitis (defined clinically)	7 (36.8)	18 (30.5)	124 (35.6)
Mode of delivery			
Vaginal vertex	3 (15.8)	24 (40.7)	102 (29.3)
Vaginal breech	4 (21.1)	6 (10.2)	18 (5.2)
Cesarean section	12 (63.2)	29 (49.2)	227 (65.2)
Infant Hemoglobin[2]; median (IQR)	12.2 (11.1, 14.6)	14.2 (12.7, 15.4)	13.8 (12.2 15.3)
Infant male sex	16 (84.2)	32 (54.2)	174 (50.0)
Gestational Age			
23 – 24 weeks stratum	13 (68.4)	34 (57.6)	104 (29.9)
25 – 26 weeks stratum	6 (31.6)	25 (42.4)	244 (70.1)
Birth Weight (g); median (IQR)	620 (542, 720)	690 (585, 785)	744 (640, 870)
Proportion < 10th Centile birth weight[3]	4 (21.1)	7 (11.9)	42 (12.1)
Time of Cord Clamping			
Immediate: 0-15 seconds	14 (73.7)	28 (47.5)	234 (67.2)
Delayed: >15 seconds	5 (26.3)	31 (52.5)	114 (32.8)
Multiple birth status			
Single	14 (73.7)	43 (72.9)	254 (73.0)
Twin	5 (26.3)	15 (25.4)	88 (25.3)
Triplet	0	1 (1.7)	6 (1.7)

[1] Other race consisted of mixed (n=7), North American Indian (n=6), Hawaiian/Pacific Islander (n=3), or not specified/unknown (n=32).
[2] Infant hemoglobin levels were measured via blood gas in the delivery room.
[3] Centile weights were adjusted for gestational age and gender, as per Kramer et al (2001) [48]
IQR = interquartile range

1

eTable 4. Bayesian Predictions for Final Study Outcomes

Prior probability Death Rate	Prior Sample Size Per Group	Posterior Pr (SI superior)	Posterior Pr (NRPsuperior)	Probability Indeterminate Results
0.2 both	100+100	<0.0001	0.135	0.86
0.2 both	200+200	<0.0001	0.036	0.999
0.2 both	10 + 10	<0.0001	0.36	0.64
0.2 NRP; 0.15 SI	100 + 100	<0.0001	0.016	0.92

Notes: Based on deaths from n=412 sample
Assuming final sample of 300+300= 600 children
Prior death rates are assumed a priori before start of trial.
Prior sample size reflect amount of evidence on which prior is based.