Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration

TITLE PAGE(S)

Title:

Association between oxygen saturation targeting and death or disability in extremely preterm infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration

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Key Points

Question: For extremely preterm infants, does targeting a lower oxygen saturation (85-89%) compared with a higher saturation (91-95%) result in a difference in death or major disability by 24 months' corrected age?

Findings: In a prospective meta-analysis of 4965 infants from five randomized clinical trials, there was no significant difference in the primary composite outcome of death or major disability between those treated with lower vs higher oxygen saturations (53.5% vs 51.6%). Lower oxygen targets were associated with increased death and necrotizing enterocolitis but reduced retinopathy of prematurity treatment.

Meaning: Among extremely preterm infants, there was no significant difference between lower and higher oxygen saturation targets on a composite of death or major disability; secondary endpoints may need to be considered in decision-making.

Abstract

Importance: There are potential benefits and harms of hyperoxemia and hypoxemia for extremely preterm infants receiving more or less supplemental oxygen.

Objective: To compare the effects of different pulse oximeter oxygen saturation (SpO_2) target ranges on death or major morbidity.

Design, Setting, and Participants: Prospectively planned, individual participant data meta-analysis of five randomized clinical trials (conducted 2005-2014), enrolling infants born at less than 28 weeks' gestation.

Exposure: Targeting a lower (85-89%) versus higher (91-95%) SpO_2 range.

Main Outcomes and Measures: The primary outcome was a composite of death or major disability by 18-24 months' corrected age (bilateral blindness, deafness, cerebral palsy with the Gross Motor Function Classification System (GMFCS) level 2 or higher, or Bayley-III cognitive or language score less than 85). There were 16 secondary outcomes including death, major disability, retinopathy of prematurity (ROP) requiring treatment, blindness, severe necrotizing enterocolitis (NEC).

Results: 4965 infants were randomized (2480 lower, 2485 higher): median gestational age 26 (IQR 25-27) weeks, mean birthweight 832 (SD 190) grams. The primary outcome occurred in 1191/2228 (53.5%) lower target and 1150/2229 (51.6%) higher target infants, Risk Difference (RD) 1.7%, 95% Confidence Interval (CI) -1.3–4.6%; Relative Risk (RR) 1.04, 95% CI 0.98–1.09; P=0.21. Of the 16 secondary outcomes, 11 were null, 2 significantly favored lower oxygen saturation, and 3 significantly favored higher oxygen saturation. Death occurred in 484/2433 (19.9%) lower target and 418/2440 (17.1%) higher target infants, RD 2.8% (0.6–5.0%), RR 1.17 (1.04–1.31), P=0.01. ROP treatment was administered to 220/2020 (10.9%) lower target and 308/2065 (14.9%) higher target infants, RD -4.0% (-6.1–-2.0%), RR 0.74 (0.63–

0.86), P<0.001. Severe NEC occurred in 227/2464 (9.2%) lower target and 170/2465 (6.9%) higher target infants, RD 2.3% (0.8–3.8%), RR 1.33 (1.10–1.61), P=0.003.

Conclusions and Relevance: In this prospectively planned meta-analysis involving extremely preterm infants, there was no significant difference between targeting lower compared with higher oxygen saturation on the primary composite outcome of death or major disability at 18-24 months' corrected age. There were significant differences favoring the higher oxygen target for death and for NEC, but favoring the lower oxygen target for ROP.

Introduction

Oxygen has been used in nurseries for over 70 years. In the 1950s it was shown that administering unrestricted oxygen to preterm infants significantly increased their risk of severe retinopathy of prematurity (ROP).[1] Pulse oximetry, which non-invasively estimates arterial oxygen saturation (SpO_2), is now almost universal in neonatal intensive care units. Lower oxygen levels (targeting SpO_2 at 90% or less) may reduce ROP,[2] whilst no studies predating the current investigations demonstrated impaired neurodevelopment or an increased risk of death.[1,3] Higher oxygen levels (targeting SpO_2 greater than 90%) may increase adverse pulmonary sequelae at SpO_2 levels above 95% when tested in infants who remained oxygen dependent many weeks after birth.[4,5]

A total sample size of approximately 5000 infants was required to detect the small but clinically important hypothesized difference of 4% in the primary outcome of death or major disability between lower and higher SpO_2 target ranges. In order to achieve this, the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration was formed in 2003[6] with the investigators from five separate randomized clinical trials (RCTs) prospectively planning to undertake their individual trials using similar study designs, participants, interventions, comparators and outcomes, and agreeing to provide individual participant data upon trial completion for inclusion in a meta-analysis.

Methods

Data Sources and Search Strategy

The NeOProM Collaboration was a prospectively planned, individual participant data meta-analysis of five trial groups in the USA (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial - SUPPORT 2005-11),[7] Canada (Canadian Oxygen Trial - COT 2006-12),[8] New Zealand (Benefits Of Oxygen

Saturation Targeting New Zealand - BOOST-NZ 2006-12),[9] United Kingdom (Benefits Of Oxygen Saturation Targeting II United Kingdom - BOOST-II UK 2007-14),[10] and Australia (Benefits Of Oxygen Saturation Targeting II Australia - BOOST-II AUS 2006-13).[11] These studies were considered eligible for inclusion in the meta-analysis prior to the results of any of the trials being known.[12] A study protocol was agreed and published[13] in January 2011, registered on ClinicalTrials.gov and a statistical analysis plan (SAP) agreed in September 2015 (see Supplement 1). The conduct of each trial was approved by the relevant Institutional Review Boards or Ethics Committees and written informed consent was obtained from participating parents.

Study Selection and Eligibility Criteria

All five studies[14-19] were randomized, double-blind, multi-center trials with infants eligible if they were born before 28 weeks' gestation and enrolled within 24 hours of birth. Infants were randomized within each trial to target either a lower (85%-89%) or higher (91%-95%) SpO_2 range. To ensure that parents, care-givers and outcome assessors remained masked to treatment allocation, each trial used Masimo pulse oximeters that had been modified to display and store oxygen saturations between 88% and 92% that were either 3% above or below the actual values. True values were displayed if the actual SpO_2 decreased below 84% or increased above 96%. Caregivers were instructed to adjust the concentration of inspired oxygen to maintain the displayed SpO_2 between 88% and 92%, thus producing two treatment groups with actual target saturations of either 85% to 89%, or 91% to 95% (see Supplement 2, eFigure 1). During the trials an artefact was identified in the calibration software of the oximeters that had the potential to influence the achieved oxygen saturation patterns.[20] Three of the trials (BOOST-II UK, BOOST-II Australia and COT) changed their oximeters to incorporate revised oximeter software. On advice from their Data and Safety Monitoring Committees, two trials (BOOST-II UK and Australia) were terminated by their respective Trial Steering Committees after a pooled interim analysis of mortality

data, subgrouped by oximeter software type, was undertaken[21] when 81% and 95% of their target samples, respectively, had been achieved.

Data Extraction

A list of requested variables was sent to each trial group based on the agreed (in September 2015) SAP prior to the sharing of any individual participant data for use in the combined meta-analysis. These variables included randomization and baseline characteristics (including subgroup variables), in-hospital and 18-24 month follow-up information from individual participants (see Supplement 2 for the full list of pre-specified variables). De-identified data were provided by the trial groups between March and April 2016. Data were checked for accuracy with published reports, trial protocols and data collection sheets. Inconsistencies were discussed with individual investigators and discrepancies resolved by consensus. Each trial verified its own finalized dataset prior to inclusion in the study database.

Key Outcome Definitions

The primary outcome was a composite of death or major disability at 18-24 months' corrected age. Major disability comprised any of the following: Bayley Scales of Infant and Toddler Development version 3[22] (Bayley-III) cognitive score <85 or language score <85; severe visual loss (cannot fixate or is legally blind with visual acuity <6/60 in both eyes); cerebral palsy with the Gross Motor Function Classification System level 2 or higher;[23] or deafness requiring hearing aids. When a Bayley-III assessment was unavailable, some trials used alternative sources of information for classifying cognitive delay, such as a Bayley-II Mental Developmental Index score <70, or another validated assessment tool (e.g. Griffiths test), or a pediatric assessment, or a parent-reported measure of neurodevelopmental impairment (e.g. able to speak fewer than 5-10 words). To assess the effects of inclusion of these alternate measures of disability, a pre-specified supportive analysis of the primary outcome was also undertaken (see Figure 1 footnote and Supplement 2, page 4).

Secondary outcomes were: the components of the primary outcome (death prior to 24 months' corrected age; major disability); death prior to 36 weeks' postmenstrual age; death prior to hospital discharge; the individual components of the major disability outcome (developmental delay, severe visual impairment, deafness, cerebral palsy); ROP treated by laser photocoagulation, cryotherapy, or anti- vascular endothelial growth factor injection in one or both eyes; severe necrotizing enterocolitis (NEC leading to abdominal surgery or death); oxygen treatment at 36 weeks' postmenstrual age; postmenstrual age when each of the following respiratory support measures ceased: endotracheal intubation, continuous positive airway pressure, oxygen treatment, or home oxygen (if received); patent ductus arteriosus (PDA) diagnosed by ultrasound and receiving any treatment; PDA receiving surgical treatment; weight z-scores at 36 weeks' postmenstrual age, at discharge home, and at 18-24 months' corrected age; one or more re-admissions to hospital by 18-24 months' corrected age; and time to death.

Assessing the Risk of Bias

The five trials were assessed for risk of bias using the Cochrane Collaboration domains[24] and consensus reached via discussion with the full study group.

Statistical Analysis

The pre-planned total sample size was 5230 infants. Because two trials stopped early, an individual participant data meta-analysis was undertaken of the 4965 infants recruited overall, which provided approximately 80% power (with a two-sided p-value of 0.05) to detect a minimum absolute risk difference of 4% in the primary composite outcome of death or major disability by 18-24 months' corrected age, corresponding to a minimally important number-needed-to-treat of 25 to prevent one major adverse outcome.[13] This minimal difference was derived via discussion with clinical experts, no formal assessments were undertaken.

Analysis was performed on an intention-to-treat basis using all data from each trial included in a single model. The I^2 statistic[25] was used to assess heterogeneity for all primary and secondary outcomes. No statistical methods were used to deal with the small proportion of missing data, but sensitivity analyses were undertaken for the primary outcome by using alternative measures of disability when Bayley-III outcomes were missing (see Figure 2 footnote for 'Supportive analysis' definitions). Binary endpoints were analyzed using log binomial regression in a generalized estimating equations (GEE) model with an exchangeable correlation structure to account for multiple births. Models were adjusted for trial as a fixed effect as the prospective meta-analysis methodology meant all five trials were very similar with respect to their included participants, interventions and outcome definitions. Sensitivity analyses using random effects models were also undertaken. Results were presented as risk differences (RD) and relative risks (RR) with 95% confidence intervals (CI) and two-sided p-values. If these models failed to converge, Poisson models with a robust variance estimator were used. Continuous outcomes were analyzed using linear regression in GEE models and presented as mean differences. Time to death was assessed between treatment groups using proportional hazard models and displayed using Kaplan-Meier survival curves.[26] Relative risks and hazard ratios were computed such that values greater than 1 favoured the higher target group. Subgroup analyses (gestational age (<26 weeks vs ≥26 weeks), inborn or outborn, use of any antenatal corticosteroids, sex, small for gestational age (SGA, <10th percentile), multiple birth, mode of delivery, time of intervention commencement (<6 hours vs ≥6 hours after birth), type of oximeter software (original vs revised)) were pre-specified and performed for primary and secondary outcomes by including a treatment-by-subgroup interaction term in the model. Two-sided p-values less than 0.05 were considered to indicate statistical significance, with no adjustment for multiple comparisons. Thus pre-specified secondary outcomes were interpreted cautiously (recognising the potential for Type I error) and subgroup analyses considered exploratory. Analyses were performed using SAS version 9.3.

Results

Study Identification and Selection

Data from the five included trials were collected and synthesized centrally following publication of the main results of all trials. Characteristics of the five studies are included in Supplement 1, eTable 1. Individual participant data (IPD) from 4965 infants (2480 randomized to the lower, 2485 to the higher target range), with a median gestational age of 26 (IQR 25-27) weeks and a mean birthweight of 832 (SD 120) grams, were meta-analyzed. Baseline characteristics of each of the included trials and the combined data are described in Table 1. Data were available for 90% of infants for the protocol-defined primary outcome, and for 95% of infants for the pre-specified supportive analysis of the primary outcome which used alternate measures of cognitive disability (Figure 1).

Primary outcome results

There was no significant difference between targeting a lower SpO_2 range (85-89%) compared with targeting a higher SpO_2 range (91-95%) on the primary composite outcome of death or major disability at 18-24 months' corrected age (lower 53.5%, higher 51.6%; RD 1.7%, 95% CI -1.3–4.6%; RR 1.04, 95% CI 0.98–1.09; p=0.21; I^2=14%; Figure 2). A supportive analysis of the primary outcome, which included alternate measures of disability, also showed no significant difference in the rate of death or major disability between the two groups (RD 1.7%, 95% CI -1.2–4.5%; RR 1.04, 95% CI 0.98–1.09; p=0.20; I^2=27%; Figure 2).

Secondary outcome results

Of the 16 secondary outcomes, 11 were null, 2 significantly favored lower oxygen saturation, and 3 significantly favored higher oxygen saturation. An analysis of each component of the primary outcome (Figure 2) showed that targeting the lower SpO_2 range was associated with a significantly increased

incidence of death at 18-24 months' corrected age (RD 2.8%, 95% CI 0.6–5.0%; RR 1.17, 95% CI 1.04–1.31; p=0.01; I^2=0%), but not other components including severe visual impairment (RD 0.1%, 95% CI -0.6–0.8%; RR 1.12, 95% CI 0.60–2.08; p=0.73; I^2=0%). Survival analysis also showed a significant increase in risk of death by 18-24 months for the lower target group (Hazard Ratio 1.17, 95% CI 1.03–1.34; p=0.02; see Supplement 2, eTable 2 and eFigure 2).

Results of other secondary outcomes are listed in Figure 3. These show infants in the lower target group had an increase in death at other time points (36 weeks' postmenstrual age and hospital discharge), severe NEC, and PDA treated with surgical ligation, but a lower rate of ROP receiving treatment and oxygen treatment at 36 weeks' postmenstrual age. There were no significant differences between the two groups for other secondary outcomes (Figure 2).

Subgroup analyses results

There were no differences between the two groups on the primary outcome (death or major disability) for any of the pre-specified subgroup analysis factors (gestational age, outborn, antenatal corticosteroids, sex, small for gestational age, multiple pregnancy, mode of delivery, time intervention started, oximeter software type; see Figure 4). Pre-specified subgroup analyses of major outcomes by oximeter software type (Figure 5) showed a significant difference in death by 18-24 months' corrected age for the original software (RR 1.06; 95% CI 0.91–1.23; p=0.47) versus revised software (RR 1.38; 95% CI 1.14–1.68; p=0.001), interaction test for subgroup difference p=0.03. A similar result was seen for death before hospital discharge, and for death before 36 weeks' postmenstrual age.

Further pre-specified exploration of other secondary outcomes was undertaken by subgroup analyses (see Supplement 2, eTables 3-32 for all results). The number of subgroup analyses performed was large (n=319 of which 17 (5%) were nominally significant), and the interaction p-values were not formally adjusted for multiple sub-group comparisons and are thus considered exploratory.[27] Whilst there were

some differences in some subgroups for some outcomes using bivariable analyses, there was no overall pattern indicating that any particular subgroup of infants benefited more or less from the lower, compared with the higher SpO_2targeting. There was no difference in the association with lower oxygen targeting for death at 18-24 months' corrected age by known risk factors such as early gestational age (<26 weeks), small for gestational age (<10th centile using either the pre-specified Kramer charts[28] or the post-hoc Alexander curves[29] as in the SUPPORT trial[30]), male sex or infants born outside a tertiary center (see Supplement 2, eTables 15 and 33). The association with lower oxygen targeting for severe NEC was greater for inborn infants and singletons (see Supplement 2, eTable 26). For the outcome of ROP receiving treatment, the association with lower oxygen targeting was larger in infants that commenced the intervention at less than 6 hours of age (largely driven by SUPPORT results) and for those born via cesarean section (see Supplement 2, eTable 27). There was no difference in the association with lower oxygen targeting for PDA treated surgically for any of the pre-specified subgroup variables (see Supplement 2, eTable 25). The association with lower targeting on oxygen treatment at 36 weeks' postmenstrual age was greater in infants small for gestational age (see Supplement 2, eTable 30).

Sensitivity Analyses Results and Assessments of Bias, and Heterogeneity

Sensitivity analyses exploring variations in the definition of the primary outcome (see 'Supportive analysis' in Figure 2) including a Bayley-III cognitive or language score of less than 70 or other definition variations used by the individual trials did not change the primary outcome findings. Using a random (rather than fixed) effects model gave the same conclusions for all outcomes with the exception of PDA treated with surgical ligation which became non-significant (see Supplement 2, eTable 34).
Overall, the trials were assessed as being at low risk of bias for all domains[31] (selection, performance / detection, attrition and reporting biases) and had low levels of statistical heterogeneity for most outcomes. The 'ROP receiving treatment' outcome had a high level of heterogeneity (I^2 = 80%) which

resulted from the substantially larger treatment effect of lower targeting on this outcome in the SUPPORT trial.

Discussion

In this prospectively planned individual participant data meta-analysis involving clinical trials of extremely preterm infants, there was no significant difference between targeting a lower (85-89%) versus higher SpO_2 range (91-95%) from soon after birth on the primary composite outcome of death or major disability at 18-24 months' corrected age. However, targeting the lower range was associated with more death and severe NEC and less treated ROP, but was not associated with blindness.

When evaluating outcomes within a clinical trial sample or synthesizing results from several trials in a meta-analysis, the effects associated with treatment represent averages, and the true benefits and harms may differ from those in these analyses. Further, tests of associations between treatment and secondary, albeit pre-specified and important, outcomes (including the individual components of the composite primary outcome), can be considered exploratory, and the results interpreted with caution. In particular, the statistically significant increased risk of death would not remain significant if adjusted for multiple testing. However, death was a major component of the composite primary outcome, and a clear difference in death, in either direction, was used to assess the need for early stopping in two trials.[21] The current pooled estimated risk and confidence intervals for mortality from these trials thus provide the best currently available indication to guide future clinical practice.

Pre-specified subgroup analyses showed consistent results across trials for most outcomes, except for a larger association on treated ROP within the SUPPORT trial. Reasons for this result in SUPPORT need to be explored more fully. One possible explanation for the heterogeneity is that most infants in the

SUPPORT trial were randomized before birth, but this hypothesis cannot be explored reliably in the other trials because they had too few infants recruited early.[32]

Mortality was increased in the lower target group overall, in the first reported trial that used the original software exclusively,[14] and in the subgroup analysis that was pre-specified in the study protocol (original versus revised oximeter software,[13] Figure 5, Supplement 1). There has been considerable debate among the study investigators whether the change in oximeter software was responsible for this result.[21,33-36]

A subgroup analysis undertaken by the SUPPORT trial investigators found that, in their trial, mortality in the lower target group was greater for SGA infants.[30] A pre-specified subgroup analysis using a common definition of SGA[28] across the combined dataset, and a *post-hoc* analysis on the full dataset using the same definition of SGA as used in the SUPPORT trial (Alexander curves),[29,30] did not confirm this relationship (see Supplement 2, eTable 33).

The main strength of this meta-analysis is that the five trials were planned prospectively to be similar in design and their investigators agreed to undertake a combined pooled individual participant data meta-analysis after completion, based on a protocol and analysis plan developed in advance of any trial results.[37,38] As would be expected with this study design, heterogeneity across the trials for most outcomes was low.

A previous Cochrane Review[31] had synthesized the aggregate data available from the published reports of the five trials. In contrast, these results were derived using raw, individual participant data, sourced directly from the trialists and combined centrally, making this the most comprehensive and rigorous analyses available of these data. The IPD analyses methods employed also permitted adjustment for the correlation of multiples; standardization of important outcomes across trials, including the definition of major disability; and enabled testing of the impact of differences in outcome definitions via sensitivity

analyses. Whilst the main findings are similar to some of the Cochrane Review results, the current IPD meta-analysis has provided new insights into the consistency of results across multiple subgroups which now clearly do *not* support the notion that the findings should be restricted to certain groups of infants such as those born small-for-gestational age or at very early gestations. The 2016 American Academy of Pediatrics guidelines[39] noted that their recommendations at that time were made "pending additional data, including the individual patient meta-analysis (NeOProM)." Thus these new findings should help clarify these ongoing debates.

Implications for future research may include investigations of the effects of: differences in alarm limits and targeting compliance[40] and in the level of exposure to the intervention on outcomes; measures of SpO_2 achieved and/or the proportion of time spent at various SpO_2 levels on outcomes (e.g. via prediction models adjusted for potential confounders); the oximeter software change on mortality (e.g. further explanation of why a larger association was seen in this subgroup); and, using automated methods to match the relatively narrow target ranges required.

Limitations

This study has several limitations. First, all five trials reported less separation in oxygen exposure between treatment groups than anticipated, largely because the lower saturation target groups had higher than intended saturations.[16] Second, two trials (BOOST-II UK and BOOST-II AUS) were stopped early, which may have resulted in some over-estimation of the effect on mortality in these trials.[41] However, excluding truncated studies from meta-analyses can lead to substantial bias due to underestimation of overall treatment effects.[42] Therefore, the best estimate of the association with treatment remains the overall combined results from the five trials. Third, the lack of an association of oxygen target range on blindness, but with a clear difference on ROP by treatment group, may change

with longer follow-up, when less severe visual impairments may become apparent. Fourth, the potential for false positive results based on multiple comparisons from 16 secondary outcomes and hundreds of subgroup analyses means that individual comparisons, although nominally significant, should be considered exploratory and interpreted cautiously. Fifth, whilst these results are generalizable across the five trials, caution should be exercised not to extend these findings to other settings which do not have early screening for ROP, appropriate ROP treatment or skilled nursing care regarding alarm limits. The trials studied the effects of SpO_2 target ranges, not oximeter alarm limits, and these two concepts are not interchangeable.

Conclusion

In this prospectively planned individual participant data meta-analysis involving extremely preterm infants, there was no significant difference between targeting lower oxygen saturation compared with higher saturation on the primary composite outcome of death or major disability at 18-24 months' corrected age. There were significant differences favoring the higher oxygen target for death and for NEC, but favoring the lower oxygen target for ROP.

Article information

Corresponding Author: Askie.

Author Contributions: Drs Askie and Davies had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors contributed to the study concept and design.

Acquisition, analysis, or interpretation of data: Drs Davies and Askie acquired and analysed the data from the included trials. All authors were involved in the interpretation of the data.

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Figure labels and legends

Figure 1

Title:

Participant flow chart

Legend:

^ Primary outcome as pre-specified in published NeOProM protocol: composite outcome of death or major disability by 18-24 months' age, corrected for prematurity. Major disability is any of the following: Bayley-III Developmental Assessment cognitive score <85 and/or language score <85; severe visual loss; cerebral palsy with Gross Motor Function Classification System (GMFCS)[22] level 2 or higher at 18-24 months' age, corrected for prematurity; or deafness requiring hearing aids.

[#] Supportive analysis of primary outcome: including using alternative sources of information for classifying major disability as used within individual trials. This may have included a Bayley-II Mental Developmental Index (MDI) score <70, or another validated assessment tool (e.g. Griffiths test), or a pediatrician assessment, or parent-reported measure of neurodevelopmental impairment (e.g. able to speak less than 5-10 words) or other measures.

[+] Maximum number infants available for major disability assessment at 18-24 months (denominator) and components was 3,971 as 902 infants were known to have died by 18-24 months, and a further 92 infants had unknown death status at this time point, and could not be assessed for major disability outcomes.

Figure 2

Title:

Effect of oxygen saturation targeting on composite primary outcome (death or major disability) and components at 18-24 months' corrected age

Legend:

a Major disability (per protocol)

b Major disability (using supplementary data)

c Bayley III Developmental Assessment cognitive or language score <85

d Cerebral palsy with GMFCS[22] (Gross Motor Function Classification System) ≥2 (higher levels = functioning more impaired), or cerebral palsy diagnosed but GMFCS unknown

e Deafness requiring hearing aids, or worse

f Severe visual impairment, as defined by trialists

Box sizes correspond to precision (the more precise the larger the box)

^ Primary outcome as pre-specified in published NeOProM protocol: composite outcome of death or major disability by 18-24 months' age, corrected for prematurity. Major disability is any of the following: Bayley-III Developmental Assessment cognitive score <85 and/or language score <85; severe visual loss; cerebral palsy with GMFCS[22] level 2 or higher at 18-24 months corrected age; or deafness requiring hearing aids.

Supportive analysis of primary outcome: including using alternative sources of information for classifying major disability as used within individual trials. This may have included a Bayley-II MDI score <70, or another validated assessment tool (e.g. Griffiths test), or a paediatrician assessment, or parent-reported measure of neurodevelopmental impairment (e.g. able to speak less than 5-10 words) or other measures.

Figure 3

Title:

Effect of oxygen saturation targeting on secondary outcomes

Legend:

a PMA = postmenstrual age (weeks)

b diagnosed by ultrasound and receiving medical or surgical treatment during initial hospitalization

c diagnosed by ultrasound and receiving surgical treatment during initial hospitalization

d before 18-24 months corrected age

e receiving surgery or leading to death during initial hospitalization

f corrected age

g with endotracheal tube

h without endotracheal tube

i without positive airway pressure

Box sizes correspond to precision (the more precise the larger the box)

Denominators include the total number of infants with a known outcome. Hence for some outcomes, for example, the PMA when home oxygen was ceased, data can only be calculated using the 537 infants who received home oxygen and for whom the PMA when ceased is known.

Figure 4

Title:

Subgroup analyses of primary outcome (composite of death or major disability)

Legend:

a Subgroup analysis by oximeter software type (original versus revised) excluded n= 74 infants in COT who were exposed to both the original and revised software.

b Inborn - born inside the treating center; Outborn - born outside the treating center (e.g. transferred from another hospital)

c Less than 10th percentile using charts from Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population based Canadian reference for birth weight for gestational age. Pediatrics. 2001;108(2):E35.

Box sizes correspond to precision (the more precise the larger the box)

Denominators include the total number of infants with a known outcome.

Figure 5

Title:

Subgroup analysis by oximeter software type

Legend:

a months corrected for prematurity

b Bayley III Developmental Assessment cognitive or language score <85

c Cerebral palsy with GMFCS[22] ≥2 (if known) or with GMFCS unknown

d Deafness requiring hearing aids, or worse

e Severe visual impairment as defined by trialists

f Postmenstrual age

g Patent ductus arteriosus (PDA) diagnosed by ultrasound and receiving medical or surgical treatment

h Patent ductus arteriosus (PDA) receiving surgical treatment

i Retinopathy of prematurity (ROP)

j Necrotizing enterocolitis (NEC) receiving surgery or leading to death

k one or more

Denominators include the total number of infants with a known outcome.

This subgroup analysis by oximeter software type excludes n=74 infants in COT who were exposed to both the original and revised software.

Box sizes correspond to precision (the more precise the larger the box)

Table 1: Baseline Characteristics

	SUPPORT [14,15] (N=1316)	COT[16] (N=1201)	BOOST-NZ[17] (N=340)	BOOST-II UK[18,19] (N=973)	BOOST-II AUS[18,19] (N=1135)	Overall	
						Lower SpO_2 Target (N=2480)	Higher SpO_2 Target (N=2485)
Mothers at birth							
Use of antenatal corticosteroids, N(%)							
None	50 (3.8)	131 (10.9)	38 (11.2)	88 (9.0)	106 (9.3)	215 (8.7)	198 (8.0)
Partial course[a]	326 (24.8)	259 (21.6)	89 (26.2)	272 (28.0)	293 (25.8)	609 (24.6)	630 (25.4)
Full course	939 (71.4)	807 (67.4)	213 (62.6)	607 (62.4)	727 (64.1)	1648 (66.5)	1645 (66.3)
Mode of delivery, N (%)							
Vaginal – normal	433 (32.9)	462 (38.6)	149 (43.8)	593 (61.1)	511 (45.0)	1064 (43.0)	1084 (43.7)
Vaginal – instrumental	0 (0)	3 (0.3)	5 (1.5)	0 (0)	18 (1.6)	10 (0.4)	16 (0.6)
Caesarean	883 (67.1)	732 (61.2)	186 (54.7)	378 (38.9)	600 (52.9)	1400 (56.5)	1379 (55.5)
Infants at birth							
Birth weight (g), mean (sd)	830 (193)	837 (193)	879 (194)	821 (185)	825 (184)	829 (187)	836 (192)
Female, N(%)	604 (45.9)	546 (45.5)	160 (47.1)	456 (46.9)	546 (48.1)	1169 (47.1)	1143 (46.0)
Gestational age (weeks) , median (IQR)	26.3 (25.3, 27.1)	26.0 (25.0, 27.0)	26.2 (25.2, 27.0)	26.1 (25.0, 27.1)	26.1 (25.1, 27.0)	26.0 (25.0, 27.0)	26.0 (25.0, 27.0)
<26 weeks, N(%)	565 (42.9)	512 (42.6)	144 (42.4)	431 (44.3)	481 (42.4)	1063 (42.9)	1070 (43.1)
≥26 weeks, N(%)	751 (57.1)	689 (57.4)	196 (57.6)	542 (55.7)	654 (57.6)	1417 (57.1)	1415 (56.9)
Small for gestational age, N(%)							
Trialists defined[b]	96 (7.3)	105 (8.7)	30 (8.8)	147 (15.2)	158 (13.9)	267 (10.8)	269 (10.8)
NeOProM defined[c]	210 (16.0)	105 (8.7)	30 (8.8)	113 (11.6)	158 (13.9)	302 (12.2)	314 (12.6)
Apgar score at 5 minutes, median (IQR)[d]	7 (6, 8)	7 (6, 8)	8 (6, 9)	-	7 (6, 8)	7 (6, 8)	7 (6, 8)
Admission temperature (°C), mean (sd)	36.2 (0.9)	36.4 (0.9)	36.4 (1.0)	36.6 (0.9)	36.0 (1.0)	36.3 (1.0)	36.3 (0.9)
Inborn[e], N(%)	1316 (100.0)	1105 (92.0)	316 (92.9)	854 (88.0)	1049 (92.4)	2327 (93.9)	2313 (93.1)
Inspired oxygen concentration immediately prior to randomization (%), median (IQR)[d,f]	-	21 (20, 25)	21 (21, 25)	-	21 (21, 24)	21 (21, 25)	21 (21, 25)
Infants at randomization							
Oximeter calibration software, N(%)							

	SUPPORT [14,15] (N=1316)	COT[16] (N=1201)	BOOST-NZ[17] (N=340)	BOOST-II UK[18,19] (N=973)	BOOST-II AUS[18,19] (N=1135)	Overall	
						Lower SpO_2 Target (N=2480)	Higher SpO_2 Target (N=2485)
Original	1316 (100.0)	564 (47.0)	340 (100.0)	228 (23.4)	692 (61.0)	1569 (63.3)	1571 (63.2)
Revised	0 (0)	563 (46.9)	0 (0)	745 (76.6)	443 (39.0)	879 (35.4)	872 (35.1)
Mixed	0 (0)	74 (6.2)	0 (0)	0 (0)	0 (0)	32 (1.3)	42 (1.7)
Time intervention started, N(%)[d]							
<6 hours	1283 (99.2)	53 (4.4)	56 (16.5)	-	119 (10.5)	752 (38.0)	759 (38.3)
Positive airway pressure with endotracheal tube, N(%)[d,g]	835 (63.9)	925 (77.0)	230 (67.6)	-	714 (63.0)	1337 (67.3)	1367 (68.5)
Positive airway pressure without endotracheal tube, N(%)[d,h]	449 (34.4)	242 (20.1)	109 (32.1)	-	410 (36.2)	621 (31.3)	589 (29.5)
Oxygen treatment without positive airway pressure, N(%)[d]	11 (0.8)	3 (0.2)	0(0)	-	1 (0.1)	9 (0.5)	6 (0.3)
No respiratory support, N(%)[d]	12 (0.9)	31 (2.6)	1 (0.3)	-	9 (0.8)	20 (1.0)	33 (1.7)

[a]Mother did not receive the full 2 doses a full 48 hours before birth [b]Trialist defined: using trial-specific small for gestational age definitions [c]NeOProM definition: less than 10th percentile using charts from Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population based Canadian reference for birth weight for gestational age. *Pediatrics* 2001; 108(2):E35

[d]Not available for BOOST-II UK [e]Born in the treating center [f]Not available for SUPPORT [g]Includes all forms of positive pressure ventilation delivered via an endotracheal tube

[h]Includes all other forms of respiratory support including Continuous Positive Airway Pressure (CPAP) and nasal cannula oxygen (high or low flow)

Denominators include the total number of infants with a known outcome