NeOProM

Neonatal Oxygenation Prospective Meta-analysis Collaboration study

Statistical Analysis Plan

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Final version, date: 9th September 2015

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1 Introduction and overview

1.1 Study overview

1.1.1 Study design

To detect a small but important 4% increase in death or severe disability in survivors, approximately 5000 neonates would need to be recruited. As extreme prematurity affects 1% of births, such a project undertaken by one trial group would be prohibitively lengthy and expensive. Hence, the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration has been formed. A prospective meta-analysis (PMA) is one where studies are identified, evaluated, and determined to be eligible before the results of any included studies are known or published, thereby avoiding some of the potential biases inherent in standard, retrospective meta-analyses. This methodology provides the same strengths as a single large-scale multicentre randomised study whilst allowing greater pragmatic flexibility. The NeOProM Collaboration protocol (NCT01124331) was agreed prior to the results of individual trials being available. Each trial will first publish their respective results as they become available and the combined meta-analytic results, using individual participant data (IPD), will be published when all trials are complete.

1.1.2 Primary objective

The primary question to be addressed by this study is: compared with a functional oxygen saturation level (SpO₂) of 91-95%, does targeting SpO₂ 85-89% in extremely preterm infants from birth or soon after birth, result in a difference in mortality or major disability in survivors by 2 years corrected age (defined as gestational age plus chronological age minus 40 (in weeks))? 

1.1.3 Patient population

Participants in the eligible trials will be infants born before 28 weeks’ gestation and enrolled within 24 hours of birth.

1.1.4 Interventions

Babies were randomised within each trial to receive either a lower (SpO₂ 85-89%) or higher (SpO₂ 91-95%) functional oxygen saturation target range from soon after birth, for durations specified in each trial protocol. Assignment was masked to parents, care-givers and outcome assessors by the use of pulse oximeters that were adjusted to display either 3% above or below the infant’s actual saturation value within the displayed 88-92% oxygen saturation range, with a tapered offset when the displayed oxygen saturation was 85-87% and 93-95%. Actual oxygen saturation values above 95% and below 85% were not adjusted, and were always displayed as actual values.
1.1.5 Sample size

Compared with a functional oxygen saturation level (SpO₂) of 91-95%, targeting SpO₂ 85-89% within 24 hours of birth is associated with <4% absolute risk difference from 42% to 46% or from 42% to 38% (10% relative risk increase or reduction (RR)) in mortality or major disability by 2 years corrected age.

The total projected sample size of 5230 infants randomised into the SUPPORT, BOOST-II Australia, BOOST-NZ, BOOST-II UK, COT trials (see Appendix A for trial details) would have 80% power (2p=0.05) to detect a difference of at least 3.8 % (for example from 42% to 45.8%) in the primary outcome: death or major disability. The actual sample size of 4959 recruited to these studies will have 80% power to detect a minimum of 4% difference. All these studies have been registered on recognised clinical trials registries. This prospective meta-analysis thus comprises the five randomised trials which address this and other clinically important questions.

1.1.6 Contact details

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Prof Barbara Schmidt  
Prof William Tarnow-Mordi

1.2 Data collection

The Principal Investigators of the participating trials have pledged their support for a prospective meta-analysis (PMA) of individual participant data (IPD) from each of these studies. These five trials are sufficiently similar in terms of the population enrolled, interventions tested and outcomes measured to allow the collection and combination of IPD from each trial into a common dataset.
1.3 Definition of safety and efficacy variables

1.3.1 Endpoints

Primary:
- Composite outcome of death or major disability by 18-24 months corrected age. Major disability is defined as any of the following:
  - Bayley-III Developmental Assessment cognitive score <85 and/or language score <85*
  - Severe visual loss according to trialists’ definition
  - Cerebral palsy with Gross Motor Function Classification System (GMFCS) level 2 or higher
  - Deafness requiring hearing aids
* For infants who have only a language or cognitive score but not both scores, presence or absence of neurodevelopmental impairment can be classified on the basis of one score only.

Supportive analysis of the Primary Outcome:
- Composite outcome of death or major disability by 18-24 months corrected age using a <85 Bayley-III cutpoint for cognitive and/or language scores, or if a Bayley-III cognitive or language score was not available, an analysis using either:
  i) an alternative age-standardised tool for measuring cognitive function to assess major neurodevelopmental impairment, which could include a Bayley-II MDI score <70, or another validated assessment tool (e.g. Griffiths, WPPSI test), or a personal assessment by a paediatrician; or
  ii) a parent-reported measure of neurodevelopmental impairment (e.g. able to use less than 5-10 words) if neither a Bayley-III cognitive or language score nor any measures listed in i) were available.

Secondary:
- Composite outcome of death or major disability by 18-24 months corrected age as per the primary outcome but using a <70 Bayley-III cutpoint for cognitive and/or language scores
- Retinopathy of prematurity (ROP) treatment by laser photocoagulation or cryotherapy or anti-VEGF injection
- Measures of respiratory support, including the following separate outcomes: a. oxygen treatment at 36 weeks postmenstrual age, b. postmenstrual age when ceased endotracheal intubation, c. postmenstrual age when ceased continuous positive airway pressure (CPAP), d. postmenstrual age when ceased oxygen treatment, e. postmenstrual age ceased home oxygen (if received).
- Patent ductus arteriosus diagnosed by ultrasound and receiving any treatment
- Patent ductus arteriosus receiving surgical treatment
- Necrotising enterocolitis receiving surgery or leading to death
- Weight z-score at 36 weeks’ postmenstrual age, at discharge home (based on UK less than 32 weeks’ population percentile charts) and 18-24 months corrected age (using WHO charts)
- One or more re-admissions to hospital by 18-24 months corrected age
- Major disability by 18-24 months corrected age (defined as per the primary outcome and supportive analysis of primary outcome definitions above)
- Bayley-III Developmental Assessment cognitive score <85 and/or language score <85
- Cerebral palsy with GMFCS level 2 or higher at 18-24 months corrected age
- Severe visual impairment as defined by trialists by 18-24 months corrected age
- Deafness requiring hearing aids
- Time to death
- Death prior to 36 weeks postmenstrual age, prior to hospital discharge and prior to 24 months corrected age

1.3.2 Composite outcome of death or major disability by 18-24 months corrected age

All survivors at 18-24 months corrected age will have their outcomes determined by individual(s) blinded to the child’s oxygen target. Major disability includes incidence of cerebral palsy and an assessment of vision, hearing and cognitive and language delay.

**Definition:**

**Major disability** - defined as any of the following:
- Bayley-III Developmental Assessment cognitive score <85 and/or language score <85
- Severe visual impairment as defined by trialists
- Cerebral palsy with Gross Motor Function Classification System (GMFCS) level 2 or higher at 18-24 months postmenstrual age
- Deafness requiring hearing aids or worse

All infants will have their assessment classified as outlined below:

**Definition:**

**Death or major disability by 18-24 months (corrected age)** = ‘1’ if major disability or death at 18-24 months corrected age, ‘0’ if alive with no major disability.

**Death or major disability by 18-24 months (corrected age) rate** = % of patients classified as ‘1’ / total number of patients with known outcome.

If at least one disability is known, then the outcome is assigned as present; if the patient is alive and developmental delay, CP, blindness and deafness are known to be absent then the outcome is assigned as absent. For incomplete assessments with no known disabilities, the outcome will be assigned as unknown.
1.3.3 Major disability by 18-24 months corrected age

All survivors at 18-24 months corrected age will have their outcomes determined by individual(s) blinded to the child’s oxygen saturation target. Major disability includes incidence of cerebral palsy and an assessment of vision, hearing, and cognitive and language delay.

**Definition:**

**Major disability** - defined as any of the following:
- Bayley-III Developmental Assessment cognitive score <85 and/or language score <85
- Severe visual impairment as defined by trialists
- Cerebral palsy with Gross Motor Function Classification System (GMFCS) level 2 higher at 18-24 months postmenstrual age
- Deafness requiring hearing aids or worse

All infants will have their assessment classified as outlined below:

**Definition:**

**Major disability by 18-24 months (corrected age)** = ‘1’ if major disability by 18-24 months corrected age, ‘0’ if alive with no major disability.

**Major disability by 18-24 months (corrected age) rate** = % of patients classified as ‘1’ / total number of patients with known outcome.

If at least one disability is known, then the outcome is assigned as present; if the patient is alive and developmental delay, CP, blindness and deafness are known to be absent then the outcome is assigned as absent. For incomplete assessments with no known disabilities, the outcome will be assigned as unknown.

1.3.4 ROP treatment

ROP treatment (including laser photocoagulation, cryotherapy, anti-VEGF e.g. bevacizumab) will be classified as outlined below. Infants are defined as at risk of developing ROP based on a valid assessment of ROP, as defined by individual study criteria.

**Definition:**

**ROP treatment incidence**

1. Number of infants receiving ROP treatment / number of infants at risk to develop ROP, assessed by 18-24 months (corrected age).
2. Number of deaths or infants receiving ROP treatment / number of deaths plus number of surviving infants at risk to develop ROP, assessed by 18-24 months (corrected age).
1.3.5 Measures of respiratory support
Respiratory support will be assessed with the following separate measures:

**Definition:**

**Measures of respiratory support (separate outcomes)**
- Incidence of supplemental oxygen use at 36 weeks' postmenstrual age
- Incidence of supplemental oxygen use at 36 weeks' postmenstrual age using an oxygen saturation based test
- Postmenstrual age at last use of endotracheal intubation
- Postmenstrual age at last use of continuous positive airway pressure (CPAP)
- Postmenstrual age at last supplemental oxygen use
- Postmenstrual age at last home oxygen use

1.3.6 Patent ductus arteriosus receiving any treatment

Proportions of infants with patent ductus arteriosus (PDA) receiving any specific PDA treatment will be determined in each treatment arm. All randomised infants are considered at risk of developing PDA.

**Definition:**

**Patent ductus arteriosus (PDA) receiving any treatment rate**
- 1. Number of infants with PDA receiving any treatment / number of infants at risk to develop PDA.
- 2. Number of deaths of infants with PDA receiving any treatment / number of deaths plus number of surviving infants at risk to develop PDA.

1.3.7 Patent ductus arteriosus receiving surgical treatment

Proportions of infants with patent ductus arteriosus (PDA) receiving surgical treatment for PDA will be determined in each treatment arm. All randomised infants are considered at risk of developing PDA.

**Definition:**

**Patent ductus arteriosus (PDA) receiving surgical treatment rate**
- 1. Number of infants with PDA receiving surgical treatment / number of infants at risk to develop PDA.
- 2. Number of deaths or infants with PDA receiving surgical treatment / number of deaths plus number of surviving or infants at risk to develop PDA.
1.3.8  Necrotising enterocolitis requiring surgery or leading to death

Proportions of infants with necrotising enterocolitis (NEC) requiring surgery or leading to death will be determined in each treatment arm. All randomised infants are considered at risk of developing NEC.

**Definition:**

**Necrotising enterocolitis (NEC) requiring surgery or leading death rate**

1. Number of infants with NEC requiring surgery or leading to death / number of infants at risk to develop NEC.

2. Number of deaths or infants with NEC requiring surgery or leading to death / number of deaths plus number of surviving infants at risk to develop NEC.

1.3.9  Weight z-score

Weight z-score will be assessed at: 36 weeks’ postmenstrual age, discharge home (using Cole UK percentile charts)³ and 18-24 months corrected age (using WHO percentile charts)⁴.

1.3.10 Re-admissions to hospital up to 18-24 months corrected age

Proportions of infants with one or more re-admissions to hospital up to 18-24 months corrected age will be determined in each treatment arm:

**Definition:**

**Re-admissions to hospital rate**

1. Number of infants with one or more re-admissions to hospital / number of infants at risk to have re-admissions to hospital, assessed at 18-24 months corrected age.

2. Number of deaths or infants with one or more re-admissions to hospital / number of deaths plus number of surviving infants at risk to have re-admissions to hospital, assessed at 18-24 months corrected age.

Reasons for the re-admissions will be categorised.

1.3.11 Cerebral palsy at 18-24 months corrected age

Severity of cerebral palsy will be classified using Gross Motor Function Classification System (GMFCS).

* Gross Motor Function Classification System (GMFCS)

The Gross Motor Function Classification System (GMFCS) is a 5 level classification system that describes the gross motor function of children and youth with cerebral palsy on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility. Distinctions between levels are based on functional abilities, the need for assistive technology,
including hand-held mobility devices (walkers, crutches, or canes) or wheeled mobility, and to a much lesser extent, quality of movement.

The GMFCS classification system for children before 2 years (corrected age) is as follows:

- **Level I**: Infants move in and out of sitting and floor sit with both hands free to manipulate objects. Infants crawl on hands and knees, pull to stand and take steps holding on to furniture. Infants walk by 18 months and 2 years of age without the need for any assistive mobility device.
- **Level II**: Infants maintain floor sitting but may need to use their hands for support to maintain balance. Infants creep on their stomach or crawl on hands and knees. Infants may pull to stand and take steps holding on to furniture.
- **Level III**: Infants maintain floor sitting when the low back is supported. Infants roll and creep forward on their stomachs.
- **Level IV**: Infants have head control but trunk support is required for floor sitting. Infants can roll to supine and may roll to prone.
- **Level V**: Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll.

Proportions of infants with cerebral palsy with a Gross Motor Function Classification System (GMFCS) level 2 at 18-24 months corrected age will be determined in each treatment arm:

**Definition:**

**Cerebral palsy at 18-24 months corrected age rate**

1. Number of infants with cerebral palsy (Gross Motor Function Classification System (GMFCS) level 2 or higher) / number of infants at risk to develop cerebral palsy, assessed at 18-24 months corrected age.
2. Number of deaths or infants with cerebral palsy (Gross Motor Function Classification System (GMFCS) level 2 or higher) / number of deaths plus number of surviving infants at risk to develop cerebral palsy, assessed at 18-24 months corrected age.

1.3.12 *Severe visual impairment at 18-24 months corrected age*

Proportions of infants with severe visual impairment will be determined in each treatment arm:

**Definition:**

**Severe visual impairment at 18-24 months corrected age rate**

1. Number of infants with severe visual impairment as defined by trialists / number of infants at risk to develop severe visual impairment, assessed at 18-24 months corrected age.
2. Number of deaths or infants with severe visual impairment as defined by trialists / number of deaths plus number of surviving infants at risk to develop severe visual impairment, assessed at 18-24 months corrected age.
1.3.13 Deafness requiring hearing aids

Proportions of infants with deafness requiring hearing aids will be determined in each treatment arm:

**Definition:**

**Deafness rate**

1. Number of infants requiring hearing aids / number of infants at risk to develop deafness, assessed at 18-24 months corrected age.

2. Number of deaths or infants requiring hearing aids / number of deaths plus number of surviving infants at risk to develop deafness, assessed at 18-24 months corrected age.

1.3.14 Bayley-III Scales of Infant and Toddler Development

The Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III; Bayley, 2005) may be used to identify developmental delays, chart a child’s progress, and teach parents about the child’s development. It is designed to be used with children aged 1 month to 42 months. It consists of five scales:

- Cognitive
- Language (Receptive and Expressive)
- Motor (Fine and Gross)
- Social-emotional
- Adaptive behaviour (Conceptual, Social, and Practical)

It yields raw scores, composite scores and percentiles ranks, growth and developmental age scores for Cognitive, Language and Motor. The highest possible scaled score on a subset is 19, and the lowest possible scaled score is 1.

**Definition:**

**Quantitative Bayley-III scores** = summary scores (composite cognitive or language score), as reported by an assessor at 18-24 months corrected age, in each treatment arm.

For children who could not be tested because of severe developmental delay or severe autism and in whom it was thus impossible to calculate a score, a score of less than 40 will be imputed for both the cognitive and language scales.

1. Mean Bayley-III cognitive score
2. Mean Bayley-III language score
3. Number of infants with Bayley-III cognitive score <85 / number of infants with available Bayley-III cognitive score <85 assessed at 18-24 months corrected age
4. Number of infants with Bayley-III language score <85 / number of infants with available Bayley-III language score <85 assessed at 18-24 months corrected age
1.3.15 Death

Proportions of deceased infants will be determined in each treatment arm

**Definition:**

- **Death rate to 36 weeks’ postmenstrual age** = % of deaths reported at 36 weeks’ postmenstrual age / total number of infants
- **Death rate to discharge home** = % of deaths reported by discharge home / total number of infants
- **Death rate** = % of deceased patients reported at 18-24 months corrected age / total number of infants

Overall survival (OS) will be measured from date of randomisation to the study to date of death from any cause. Infants remaining alive or lost to follow-up will be censored at the last “known alive” date, i.e. the date of discharge, an intermediate contact date or the follow-up target date for the individual trial.

**Definition:**

- **Overall Survival** (months) = Number of days between date of death (or date of last contact for alive infants) and date of randomisation / 365.25 * 12
- **Status**
  - = 1 if deceased
  - = 0 if alive or lost to follow-up (censored)
2.1 Analysis overview

2.1.1 Analysis population

Analysis will be based on all infants randomised for whom an outcome is available (according to the appropriate definition). This will be referred to as the intention to treat population.

2.1.2 Analysis plan

2.1.2.1 Primary analysis

An individual participant data (IPD) analysis will be performed. For each of the primary and secondary outcomes, a one stage approach to analysis will be taken so that the individual participant data from all eligible trials are included in a single model. Fitting a model for each outcome variable will enable the variation across trials to be accounted for within the model by including a fixed trial effect. A treatment-by-trial interaction term will be tested to assess heterogeneity of treatment effect across trials. If excessive statistical heterogeneity in treatment effect or inconsistency across trials is detected (i.e. if the trial by treatment interaction term is significant), then the rationale for combining trials will be questioned and the source of heterogeneity explored. Random effects models including a random trial effect will be used in sensitivity analyses for all the primary outcomes.

Binary outcomes will be analysed using log-binomial regression models and results will be presented as risk ratios with 95% confidence intervals (CI) and associated two-sided p-values. If the model does not converge, log Poisson regression models with robust variance estimation will be used (Zou, 2004). Continuous outcomes will be analysed using linear regression models and results will be presented as differences in means with 95% CI and two-sided p values. Data transformations are not planned to correct for departures from normality, since the sample size is expected to be sufficient for the central limit theorem to apply (Lumley et al., 2002). Correlation between outcomes due to multiple births will be taken into account using generalized estimating equations. For the purpose of the analysis, the lower target range group will be considered the intervention/treatment group and the higher target range group will be considered the control group.

2.1.2.2 Sensitivity analysis

A sensitivity analysis of the primary outcome will be a pooled analysis of the relative risk from each trial and the 95% CI. These relative risks will include any trial specific adjustments made. The pooled analyses will then be these relative risks, weighted by the inverse variance from each study, using fixed effect models.

Two analyses will be performed for all of the secondary outcomes where the number of patients being considered would be different from the number originally enrolled into the trial (see definitions in section 1): one analysis will include infants with known secondary outcomes and a second analysis will be a composite of death and known secondary outcomes. The proportion of unknowns will be reported by treatment group but will not be included in the calculation for the event rate.
2.1.2.3 Subgroup analysis

The size of the treatment effect (lower vs higher oxygen saturation targeting) may differ by certain characteristics of either the infant or the way the intervention was delivered. These possible effects will be explored by subgroup analyses of the following characteristics.

- **Gestational age**
  - less than 26 weeks
  - greater than or equal to 26 weeks

- **Inborn or outborn**

- **Use of any antenatal corticosteroids** = yes if any of the following
  - incomplete, less than 24 hours before birth
  - complete
  - more than 7 days before birth
  - started less than 24 hours before birth
  - started 24 hours or more before birth

- **Male or female sex**

- **Small for gestational age**
  - birth weight below trialist defined cut-point
  - birth weight less than 10th percentile based on UK less than 32 weeks’ population percentile charts (Cole et al, 2014)

- **Multiple or singleton birth**

- **Mode of delivery**
  - vaginal if any of the following: vaginal, vaginal-cephalic, vaginal-breech
  - caesarean if any of the following: caesarean section before onset of labour, caesarean section after onset of labour

- **Time of intervention commencement**
  - less than 6 hours after birth
  - 6 hours or more after birth

- **Oximeter calibration software**
  - original
  - revised

Subgroup analyses will be undertaken on all pre-specified primary and secondary outcomes. Any differences in treatment effect between pre-specified subgroups will be assessed by testing a treatment-by-subgroup interaction term within the model.

2.1.2.4 Exploratory analyses

Analyses exploring outcomes weighted by degree of oxygen saturation between the treatment and control groups and by accuracy of targeting achieved are planned at a later date. These will require further data that are not being collected for the current planned analyses.
2.1.3 General principles

Descriptive statistics for the evaluation parameters will be presented in summary tables, by treatment group.

Continuous variables will be summarised by the sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant.

Categorical variables will be described in terms of frequencies of each category and frequencies converted into percentages of the number of patients examined (of non-missing).

Time-to-event outcomes will be presented as Kaplan-Meier plots of the time to the first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs as appropriate. Estimates of the effect will be expressed as hazard ratios based on the proportional hazard regression models together with 95% confidence intervals.

Statistical inference:

Statistical tests will be two-sided and performed using a 5% level of significance.
There will be no adjustment for multiple comparisons.
The primary analyses for this prospective meta-analysis will use the intention-to-treat population.

2.2 Stratification balance

Table 1 – Stratification variables

<table>
<thead>
<tr>
<th></th>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Total</th>
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<tbody>
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<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
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<tr>
<td>Gestational age at birth</td>
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<td>Less than 26 weeks</td>
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<td>Greater than or equal to 26 weeks</td>
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<td>Total</td>
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</table>
2.3 Disposition of patients

Patient disposition will be displayed in a flow diagram:

Total no. of randomised patients
N = xx

Randomised to lower oxygen saturation
N = xx

No. died

Reasons for lost to follow-up

18-24 months follow up
N = xx

No. with major disability

Randomised to higher oxygen saturation
N = xx

Reasons for lost to follow-up

No. died

18-24 months follow up
N = xx

No. with major disability
2.4 Baseline characteristics

Tables of baseline characteristics of the patients enrolled in the study will be produced.

2.4.1 Summary of baseline variables – continuous variables

*Table 2 – Participant characteristics (continuous variables)*

<table>
<thead>
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<th>Variable</th>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Total</th>
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<td>Gestational age (weeks)</td>
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<td>Weight (g) at birth</td>
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<td>Mean</td>
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<td>Admission temperature (°C)</td>
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<td>Max</td>
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<td>Apgar score at 5 minutes after birth</td>
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<td>Inspired oxygen concentration (%) immediately prior to time of randomisation</td>
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<td>Mean</td>
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<td></td>
<td>Std Dev</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.4.2 Summary of baseline variables – categorical variables

Table 3 – Participant characteristics (categorical variables)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/multiple birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inborn/outborn birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inborn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outborn</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 – Clinical history at baseline

<table>
<thead>
<tr>
<th>Use of antenatal corticosteroids</th>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (partial course)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (full course)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal - normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal - instrumental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of infants if multiple birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 – Respiratory support at baseline

<table>
<thead>
<tr>
<th>Continuous Positive Airway Pressure (CPAP)</th>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation by endotracheal tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal cannulae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.5 Primary outcome

2.5.1 Death or major disability by 18-24 months corrected age

Table 6 – Primary outcome: death or major disability by 18-24 months corrected age

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Death or major disability by 18-24 months corrected age

* Primary outcome as pre-specified in published NeOProM protocol: composite outcome of death or major disability by 18-24 months corrected age (gestational age plus chronological age). 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 level 2 or higher at 18-24 months postmenstrual age; or deafness requiring hearing aids.

* values adjusted for trials and multiple births

Table 7 – Primary outcome: death or major disability by 18-24 months corrected age

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Death or major disability by 18-24 months corrected age

* 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-III 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.

* values adjusted for trials and multiple births

2.6 Secondary outcomes

2.6.1 Death or major disability by 18-24 months corrected age (B-III <70)

Table 8 – Primary outcome: death or major disability by 18-24 months corrected age

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Death or major disability by 18-24 months corrected age

* Primary outcome using definition in Table 6 but using a Bayley III Developmental Assessment cognitive score <70 and/or language score <70 cutpoint instead of <85.

* values adjusted for trials and multiple births
2.6.2 ROP treatment

Table 9 – ROP treatment

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROP treatment

* values adjusted for trials and multiple births

2.6.3 Measures of respiratory support

Table 10 – Respiratory support (binary outcomes)

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N %</td>
<td>N %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Supplemental oxygen use at 36 weeks' postmenstrual age
Supplemental oxygen use at 36 weeks' pma using oxygen saturation based test
Never received supplemental oxygen

* values adjusted for trials and multiple births

Table 11 – Respiratory support (continuous outcomes)

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Postmenstrual age at last use of endotracheal intubation
Postmenstrual age at last use of continuous positive airway pressure
Postmenstrual age at last use of supplemental oxygen
Postmenstrual age at last use of home oxygen

* values adjusted for trials and multiple births
2.6.4 Patent ductus arteriosus diagnosed by ultrasound and receiving medical or surgical treatment

*Table 16 – Patent ductus arteriosus (PDA) diagnosed by ultrasound and requiring medical or surgical treatment*

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

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

* values adjusted for trials and multiple births

2.6.5 Patent ductus arteriosus receiving surgical treatment

*Table 13 – Patent ductus arteriosus (PDA) receiving surgical treatment*

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Patent ductus arteriosus (PDA) receiving surgical treatment

* values adjusted for trials and multiple births

2.6.6 Necrotising enterocolitis receiving surgery or leading to death

*Table 14 – Necrotising enterocolitis (NEC) receiving surgery or leading to death*

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Necrotising enterocolitis (NEC) receiving surgery or leading to death

* values adjusted for trials and multiple births
2.6.7 Weight z-score

Table 15 – Weight z score

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Mean difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weight z-score
at 36 weeks’ postmenstrual age
at discharge home
at 18-24 months corrected age

* values adjusted for trials and multiple births

2.6.8 One or more re-admissions to hospital up to 18-24 months corrected age

Table 16 – One or more re-admissions to hospital

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

One or more re-admissions to hospital

* values adjusted for trials and multiple births

2.6.9 Major disability

Table 17 – Major disability by 18-24 months corrected age

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Major disability (as per protocol)^ by 18-24 months corrected age
Major disability (trialist defined)# by 18-24 months corrected age

^ as pre-specified in published NeOProM protocol: 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 level 2 or higher at 18-24 months postmenstrual age; or deafness requiring hearing aids.

# as defined by trialists - includes alternative measures of disability as described in Table 7.

* values adjusted for trials and multiple births
2.6.10  Cerebral palsy at 18-24 months corrected age

Table 18 – Cerebral palsy

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Cerebral palsy

* values adjusted for trials and multiple births

2.6.11  Severe visual impairment at 18-24 months corrected age

Table 19 – Severe visual impairment

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Severe visual impairment as defined by trialists

* values adjusted for trials and multiple births

2.6.12  Deafness requiring hearing aids

Table 20 – Deafness requiring hearing aids

<table>
<thead>
<tr>
<th>Lower Oxygen Saturation</th>
<th>Higher Oxygen Saturation</th>
<th>Adjusted* Relative Risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
</tbody>
</table>

Deafness requiring hearing aids or worse

* values adjusted for trials and multiple births
2.6.13 Quantitative Bayley–III scores

Table 21 – Quantitative Bayley-III scores

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Language</th>
<th>Receptive communication</th>
<th>Expressive communication</th>
</tr>
</thead>
</table>

* values adjusted for trials and multiple births

2.6.14 Death

Table 22 – Deaths

<table>
<thead>
<tr>
<th>Death prior to 18-24 months corrected age</th>
<th>Death prior to 36 weeks postmenstrual age</th>
<th>Death prior to discharge</th>
</tr>
</thead>
</table>

* values adjusted for trials and multiple births

Table 23 – Median survival times

<table>
<thead>
<tr>
<th>Median overall survival (months)</th>
</tr>
</thead>
</table>

* Log-rank test

Figure 1 – Kaplan-Meier Overall Survival Curves
3 Abbreviations

AE  Adverse Event
BOOST Benefits of Oxygen Saturation Targeting
BPD Broncho-Pulmonary Dysplasia
BSID Bayley Scales of Infant and Toddler Development
CLD Chronic Lung Disease
COT Canadian Oxygen Trial
CPAP Continuous Positive Airway Pressure
CRF Case Report Form
GCP Good Clinical Practice
GEE Generalised Estimating Equations
GMDS Griffiths Mental Developmental Scales
GMFCS Gross Motor Function Classification System
HR Hazard Ratio
IDSMC Independent Data and Safety Monitoring Committee
IPD Individual participant data
LLN Lower Limit of Normal Range
MACS Manual Ability Classification System
MDI Mental Development Index
NEC Necrotising Enterocolitis
NeOProM Neonatal Oxygenation Prospective Meta-Analysis
NHMRC CTC National Health and Medical Research Council Clinical Trials Centre
OS Overall Survival
PDA Patent Ductus Arteriosus
PDI Psychomotor Development Index
PMA Prospective Meta-Analysis
pma Postmenstrual age
ROP Retinopathy of Prematurity
RRR Relative Risk Reduction
SAE Serious Adverse Event
SD Standard Deviation
SGS Schedule of Growing Skills
SpO₂ Oxygen Saturation
SUPPORT Surfactant Positive Airway Pressure and Pulse Oximetry Trial
ULN Upper Limit of Normal Range
WPPSI Wechsler Preschool and Primary Scales of Intelligence
95% CI 95% Confidence Interval
4 References


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## Appendix B: Characteristics of randomised trials included in the NeOProM Collaboration

<table>
<thead>
<tr>
<th>Acronym</th>
<th>BOOST-II Australia</th>
<th>BOOST-II UK</th>
<th>BOOST-NZ</th>
<th>SUPPORT</th>
<th>COT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration #</td>
<td>ACTRN12605000055606</td>
<td>ISRCTN00842661</td>
<td>ACTRN12605000253606</td>
<td>NCT00233324</td>
<td>ISRCTN62491227</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>1200</td>
<td>1200</td>
<td>320</td>
<td>1310</td>
<td>1200</td>
</tr>
<tr>
<td>Actual</td>
<td>1135</td>
<td>973</td>
<td>340</td>
<td>1310</td>
<td>1201</td>
</tr>
<tr>
<td>Countries of recruitment</td>
<td>Australia</td>
<td>United Kingdom</td>
<td>New Zealand</td>
<td>United States of America</td>
<td>Canada, USA, Argentina, Germany, Israel, Finland, Norway</td>
</tr>
<tr>
<td>Participants</td>
<td>Infants &lt; 28 wks gestation inborn or outborn &lt; 24 hrs old</td>
<td>Infants &lt; 28 wks gestation &lt; 12 hrs old (24 hrs if outborn)</td>
<td>Infants &lt; 28 wks gestation inborn or outborn &lt; 24 hrs old</td>
<td>Infants 24-27 wks gestation, &lt; 2 hrs old</td>
<td>Infants 23 0/7-27 6/7 wks gestation &lt; 24 hrs old</td>
</tr>
<tr>
<td>Blinded?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intervention</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
<td>Lower oxygen saturation (85%-89%)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
<td>Higher oxygen saturation (91%-95%)</td>
</tr>
<tr>
<td>Intervention &amp; comparator duration</td>
<td>Oximeter applied after randomisation, asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO2 &gt; 96% in room air for 95% of time over 3 days.</td>
<td>Oximeter applied from randomisation until postmenstrual age (pma) of 36 wks or until baby was breathing air. All monitoring at any time prior to 36 wks was done using study oximeter. BPD defined at 36 wks using a physiological oxygen test.</td>
<td>Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO2 &gt; 96% in room air for 95% of time over 3 days.</td>
<td>Oximeter applied within 2 hrs following admission to NICU until infant has been in room air for 72 hrs or until 36 wks corrected age, assessed by physiologic oxygen test.</td>
<td>Oximeter applied from day of birth until a min 36 wks pma. If breathing room air without any form of respiratory assistance from 35 wks pma onward, study oximetry discontinued at 36 wks pma. If receiving any form of respiratory assistance &amp;/or oxygen therapy from 35 wks pma onward study oximetry continued until 40 wks pma. Study oximetry stopped at any time before 40 wks pma if baby discharged home (with or without respiratory assistance &amp;/or oxygen).</td>
</tr>
<tr>
<td>Primary outcome(s)</td>
<td>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following: * cognitive or language score &lt;85 on BSID-3 * severe visual loss * cerebral palsy with inability to walk at 2 yrs * deafness requiring hearing aids</td>
<td>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following: * cognitive or language score &lt;85 on BSID-3 * severe visual loss * cerebral palsy with inability to walk at 2 yrs * deafness requiring hearing aids</td>
<td>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following: * composite cognitive language score Bayley-III&lt;85 or MDI&lt;70 on the Bayley-II assessment. * severe visual loss * cerebral palsy defined as GMFCS level 2 or higher * deafness requiring hearing aids</td>
<td>1. Death or survival with neurodevelopmental impairment (defined as either cognitive score on BSID-3 &lt;70, GMFCS level 2 or higher, moderate to severe CP, hearing impairment or bilateral visual impairment) at 18-22 months corrected age. 2. Survival without severe ROP (threshold ROP and/or the need for surgical intervention).</td>
<td>Death or survival with major disability at 18-21 months corrected for gestation. Major disability defined as having any of the following: * cognitive score &lt;85 and/or language score &lt;85 on BSID-3 * severe visual loss * cerebral palsy with inability to crawl or walk independently * deafness requiring hearing aids</td>
</tr>
</tbody>
</table>
### Appendix C: Primary outcome of death or major disability at 18-24 months corrected age as defined by each trial and NeOProm Collaboration

<table>
<thead>
<tr>
<th>Acronym</th>
<th>NeOProm</th>
<th>BOOST-II Australia</th>
<th>BOOST-II UK</th>
<th>BOOST-NZ</th>
<th>SUPPORT</th>
<th>CDT</th>
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<tr>
<td>Registration #</td>
<td>NCT01124331</td>
<td>ACTRN126050000055606</td>
<td>ISRCTN00842661</td>
<td>ACTRN12605000253606</td>
<td>NCT00233324</td>
<td>ISRCTN62491227</td>
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<tr>
<td>Death</td>
<td>At 18-24 months corrected age</td>
<td>At 24 months corrected age</td>
<td>At 24 months corrected age</td>
<td>At 24 months corrected age</td>
<td>At 24 months corrected age</td>
<td>At 18 months corrected age</td>
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<tr>
<td>Cognitive or language delay</td>
<td>Composite cognitive and/or language score &lt;85 on Bayley-III</td>
<td>Composite cognitive language score Bayley-III &lt;85 or MDI &lt;70 on the Bayley-II assessment. If Bayley-III or Bayley-II are missing the final criterion were replaced by any one of the following: uses &lt;10 words; or language problems indicated on the short health assessment, delayed development by &gt;12 months, other severe impairment.</td>
<td>Combined language or cognitive score of &lt;85 using Bayley-III. Alternative measures were used in some cases including WPPSI-III, Denver Developmental Screening Test, Griffiths Mental Development Scales, Schedule of Growing Skills (SGS), PARCA-R, use of fewer than 5 words, or assessed by paediatrician or GP to have more than 6 mths developmental delay by 24 mths corrected age. Information from health professionals/parents was assessed independently by 2 assessors masked to group assignment to adjudicate cognitive outcome in a small number of cases.</td>
<td>Composite cognitive language score Bayley-III &lt;85 or MDI &lt;70 on the Bayley-II assessment. If Bayley-III or Bayley-II are missing the final criterion were replaced by any one of the following: uses &lt;10 words; or language problems indicated on the short health assessment, delayed development by &gt;12 months, other severe impairment.</td>
<td>Cognitive composite score on Bayley-III &lt;70.</td>
<td>Composite cognitive and/or language score &lt;85 on Bayley-III. A priori criteria were used to determine adequate evidence for the presence or absence of this outcome if a component was missing.</td>
</tr>
<tr>
<td>Gross motor</td>
<td>GMFCS level 2 or</td>
<td>GMFCS level 2 or higher, Severe cerebral palsy</td>
<td>GMFCS level 2 or higher,</td>
<td>Moderate to severe</td>
<td>Level 2 or higher</td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>Higher</td>
<td>As indicated on the health status or short health status assessments</td>
<td>Unable to walk without help at 2 years</td>
<td>As indicated on the health status or short health status assessments</td>
<td>Cerebral palsy defined as a non-progressive 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</td>
<td>According to GMFCS. Normal level is assigned if a child can walk 10 steps independently at 18 months</td>
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<tr>
<td>Severe hearing loss</td>
<td>Deafness requiring hearing aids</td>
<td>Requiring hearing aids, as indicated on the health status or short health status assessments</td>
<td>Deafness requiring (or too severe to benefit from) a hearing aid</td>
<td>Requiring hearing aids, as indicated on the health status or short health status assessments</td>
<td>The inability to understand oral directions of the examiner and to communicate, with or without hearing amplification</td>
<td>Prescribed hearing aids or cochlear implants</td>
</tr>
<tr>
<td>Severe visual impairment</td>
<td>Severe visual impairment as defined by trialists</td>
<td>Legal blindness, as indicated on the health status or short health status assessments</td>
<td>Severe visual loss certifiable as legally blind or partially sighted</td>
<td>Legal blindness, as indicated on the health status or short health status assessments</td>
<td>Vision worse than 20/200</td>
<td>Corrected visual acuity &lt;20/200 in the better eye</td>
</tr>
</tbody>
</table>

**Appendix D: Secondary outcomes as defined by each trial and the NeOProm Collaboration**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>NeOProm</th>
<th>BOOST-II Australia</th>
<th>BOOST-II UK</th>
<th>BOOST-NZ</th>
<th>SUPPORT</th>
<th>COT</th>
</tr>
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</table>


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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy of prematurity (ROP)</td>
<td>Retinopathy of prematurity (ROP) treatment by laser photocoagulation or cryotherapy or anti-VEGF injection</td>
<td>ROP stage ≥3 subjected to retinal surgery</td>
<td>ROP stage ≥3 or APROP</td>
<td>ROP stage ≥3 subjected to retinal surgery</td>
<td>In zone 1: stage 3 ROP, even without plus disease; in zone 2: plus disease with stage 2 ROP or plus disease with stage 3 ROP</td>
<td>ROP stage ≥3. Severe retinopathy defined as unilateral or bilateral disease of stages 4 or 5 or receipt of retinal therapy in at least 1 eye</td>
</tr>
<tr>
<td>Measures of respiratory support</td>
<td>Supplemental oxygen requirement at 36 postmenstrual age; postmenstrual age ceased endotracheal intubation, continuous positive airway pressure (CPAP), supplemental oxygen, and home oxygen (if received)</td>
<td>Stop date recorded when used for ≥30 minutes for endotracheal intubation, CPAP and supplemental oxygen. Last date of home oxygen use recorded.</td>
<td>Stop date not collected for endotracheal intubation or CPAP. Last date of home oxygen use recorded.</td>
<td>Last date recorded when used for ≥30 minutes for endotracheal intubation, CPAP and supplemental oxygen. Last date of home oxygen use recorded.</td>
<td>Stop date not collected for endotracheal intubation, CPAP or supplemental oxygen use past 36 weeks gestational age.</td>
<td>Final stop date recorded for endotracheal intubation, CPAP and supplemental oxygen including use of supplemental oxygen or positive airway pressure at home.</td>
</tr>
<tr>
<td>PDA diagnosed by ultrasound and receiving any treatment</td>
<td>PDA diagnosed by ultrasound</td>
<td>PDA diagnosed by ultrasound</td>
<td>PDA diagnosed, but not necessarily by ultrasound</td>
<td>PDA diagnosed by ultrasound</td>
<td>PDA diagnosed, but not necessarily by ultrasound</td>
<td>Any diagnosis of PDA receiving therapy</td>
</tr>
<tr>
<td>PDA receiving surgical treatment</td>
<td>PDA diagnosed by ultrasound and receiving surgical treatment</td>
<td>PDA requiring surgical ligation</td>
<td>PDA requiring surgery</td>
<td>PDA requiring surgical ligation</td>
<td>PDA requiring surgery</td>
<td>PDA requiring surgical ligation</td>
</tr>
<tr>
<td>NEC requiring surgery or leading to death</td>
<td>NEC requiring surgery or leading to death</td>
<td>NEC requiring surgery or leading to death</td>
<td>NEC requiring surgery or leading to death</td>
<td>NEC requiring surgery or leading to death</td>
<td>Modified Bell’s stage ≥2 on a scale ranging from 1-3</td>
<td>Diagnosed during surgery or by a finding of pneumatosis intestinalis, hepatobiliary gas or free intraperitoneal air on XR</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Cerebral palsy with GMFCS level 2 or higher or MACS level 2 or higher at 18-24 months corrected age</td>
<td>Cerebral palsy with GMFCS score ≥ level 2</td>
<td>Unable to walk without help at 2 years (MACS level 1 or higher) and/or GMFCS score ≥ level 2</td>
<td>Cerebral palsy with GMFCS score ≥ level 2</td>
<td>Moderate to severe cerebral palsy defined as a non-progressive disorder with abnormal muscle tone in at least one arm or leg that was</td>
<td>Level 2 or higher according to GMFCS. Normal level is assigned if a child can walk 10 steps independently at 18 months</td>
</tr>
<tr>
<td>Weight z-score</td>
<td>Weight measured in grams, z-score calculated using UK or WHO percentile charts, accounting for corrected age and gender</td>
<td>Weight measured in grams</td>
<td>Weight measured in grams</td>
<td>Weight measured in grams</td>
<td>Weight measured in grams</td>
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</tr>
<tr>
<td>Re-admissions to hospital</td>
<td>One or more re-admissions to hospital up to 18-24 months corrected age</td>
<td>Re-admissions to hospital at 2 years corrected age</td>
<td>Re-admissions to hospital until 2 years after delivery was due (and cause)</td>
<td>Re-admissions to hospital at 2 years corrected age</td>
<td>Re-admission to hospital - available for children whose family provided a standardised medical history at 18 months</td>
<td>associating with abnormal control of movement or posture and a GMFCS score ≥ 2</td>
</tr>
</tbody>
</table>