

# NeOProM

## Neonatal Oxygenation Prospective Meta-analysis Collaboration study

### Statistical Analysis Plan

**Prepared by:**

Marion Fournier, Lucy Davies, Val Gebski, Adrienne Kirby, John Simes,  
Robin Roberts, Marie Gantz, Ed Juszcak, Andy King, Lisa Askie

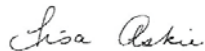
Final version, date: 9<sup>th</sup> September 2015

**Approved by Project Statistician, NHMRC Clinical Trials Centre:**



\_\_\_\_\_  
Val Gebski (Signature)  
Val Gebski (Name)  
Project Statistician (Designation)  
\_\_\_\_ 2 Feb 2016 \_\_\_\_\_ (Sign-off Date, AEST)

**Approved by Project Chair:**



\_\_\_\_\_  
Lisa Askie (Signature)  
Lisa Askie (Name)  
Project Chair (Designation)  
\_\_\_\_ 2 Feb 2016 \_\_\_\_\_ (Sign-off Date, AEST)

**Approved by:**



\_\_\_\_\_  
John Simes (Signature)  
John Simes (Name)  
Director, NHMRC Clinical Trials  
Centre, University of Sydney (Designation)  
\_\_\_\_ 24 Feb 2016 \_\_\_\_\_ (Sign-off Date, AEST)

---

## Contents

1	Introduction and overview .....	4
1.1	Study overview .....	4
1.1.1	Study design .....	4
1.1.2	Primary objective.....	4
1.1.3	Patient population .....	4
1.1.4	Interventions .....	4
1.1.5	Sample size.....	5
1.1.6	Contact details.....	5
1.2	Data collection .....	5
1.3	Definition of safety and efficacy variables .....	6
1.3.1	Endpoints .....	6
1.3.2	Composite outcome of death or major disability by 18-24 months corrected age .....	7
1.3.3	Major disability by 18-24 months corrected age .....	8
1.3.4	ROP treatment.....	8
1.3.5	Measures of respiratory support.....	9
1.3.6	Patent ductus arteriosus receiving any treatment.....	9
1.3.7	Patent ductus arteriosus receiving surgical treatment.....	9
1.3.8	Necrotising enterocolitis requiring surgery or leading to death .....	10
1.3.9	Weight z-score.....	10
1.3.10	Re-admissions to hospital up to 18-24 months corrected age .....	10
1.3.11	Cerebral palsy at 18-24 months corrected age .....	10
1.3.12	Severe visual impairment at 18-24 months corrected age .....	11
1.3.13	Deafness requiring hearing aids.....	12
1.3.14	Bayley-III Scales of Infant and Toddler Development.....	12
1.3.15	Death.....	13
2	Analysis.....	13
2.1	Analysis overview.....	14
2.1.1	Analysis population.....	14
2.1.2	Analysis plan.....	14
2.1.3	General principles.....	16
2.2	Stratification balance .....	16
2.3	Disposition of patients .....	17

---

2.4	Baseline characteristics .....	18
2.4.1	Summary of baseline variables – continuous variables .....	18
2.4.2	Summary of baseline variables – categorical variables .....	19
2.5	Primary outcome .....	20
2.5.1	Death or major disability by 18-24 months corrected age .....	20
2.6	Secondary outcomes .....	20
2.6.1	Death or major disability by 18-24 months corrected age (B-III <70) .....	20
2.6.2	ROP treatment.....	21
2.6.3	Measures of respiratory support.....	21
2.6.4	Patent ductus arteriosus diagnosed by ultrasound and receiving medical or surgical treatment.....	22
2.6.5	Patent ductus arteriosus receiving surgical treatment.....	22
2.6.6	Necrotising enterocolitis receiving surgery or leading to death .....	22
2.6.7	Weight z-score.....	23
2.6.8	One or more re-admissions to hospital up to 18-24 months corrected age.....	23
2.6.9	Major disability.....	23
2.6.10	Cerebral palsy at 18-24 months corrected age .....	24
2.6.11	Severe visual impairment at 18-24 months corrected age.....	24
2.6.12	Deafness requiring hearing aids .....	24
2.6.13	Quantitative Bayley–III scores.....	25
2.6.14	Death.....	25
3	Abbreviations.....	26
4	References .....	27
	Appendix A: List of tables and figures .....	28
	Appendix B: Characteristics of randomised trials included in the NeOProM Collaboration .....	29
	Appendix C: Primary outcome of death or major disability at 18-24 months corrected age as defined by each trial and NeOProM Collaboration .....	31
	Appendix D: Secondary outcomes as defined by each trial and the NeOProM Collaboration.....	32

---

# **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 (SpO<sub>2</sub>) of 91-95%, does targeting SpO<sub>2</sub> 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 (SpO<sub>2</sub> 85-89%) or higher (SpO<sub>2</sub> 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 (SpO<sub>2</sub>) of 91-95%, targeting SpO<sub>2</sub> 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**

**Principal Investigator:** A/Prof Lisa Askie  
NHMRC Clinical Trials Centre, University of Sydney  
Level 6, Medical Foundation Building  
92-94 Parramatta Rd  
Camperdown 2050 NSW  
Australia

**Co-Investigators:** Prof Peter Brocklehurst  
Prof Brian Darlow  
Prof Neil Finer  
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)<sup>3</sup> and 18-24 months corrected age (using WHO percentile charts)<sup>4</sup>.

### 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 of 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 10<sup>th</sup> 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

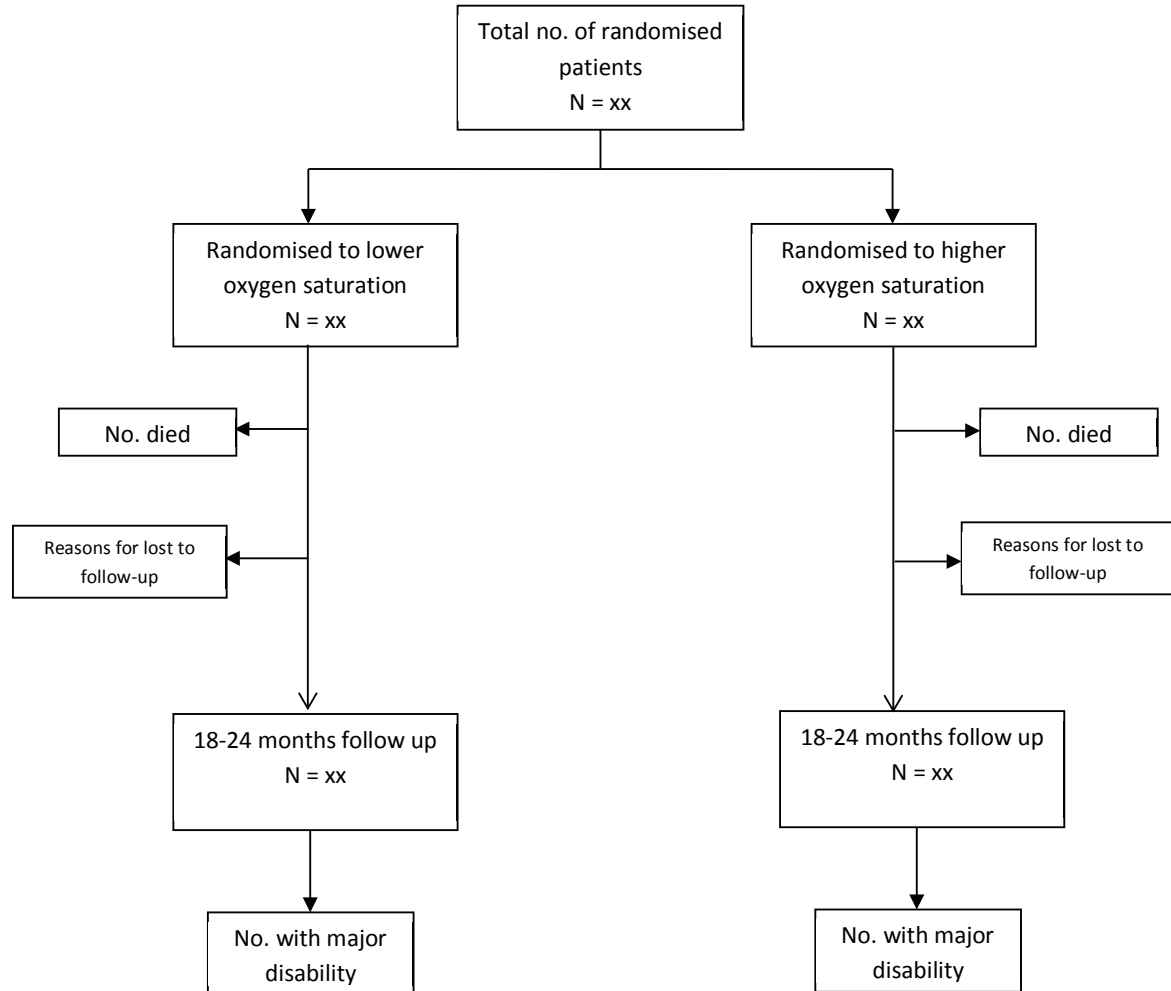
Table 1 – Stratification variables

		Lower Oxygen Saturation		Higher Oxygen Saturation		Total	
		N	%	N	%	N	%
Gestational age at birth	Less than 26 weeks						
	Greater than or equal to 26 weeks						
Trial	BOOST II Australia						
	BOOST II NZ						
	BOOST II UK						
	SUPPORT						
	COT						
Total							



## 2.3 Disposition of patients

Patient disposition will be displayed in a flow diagram:



## 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)*

		Lower Oxygen Saturation	Higher Oxygen Saturation	Total
Gestational age (weeks)	N			
	Mean			
	Std Dev			
	Median			
	Min			
	Max			
Weight (g) at birth	N			
	Mean			
	Std Dev			
	Median			
	Min			
	Max			
Admission temperature (°C)	N			
	Mean			
	Std Dev			
	Median			
	Min			
	Max			
Apgar score at 5 minutes after birth	N			
	Mean			
	Std Dev			
	Median			
	Min			
	Max			
Inspired oxygen concentration (%) immediately prior to time of randomisation	N			
	Mean			
	Std Dev			
	Median			
	Min			
	Max			

## 2.4.2 Summary of baseline variables – categorical variables

Table 3 – Participant characteristics (categorical variables)

		Lower Oxygen Saturation		Higher Oxygen Saturation		Total	
		N	%	N	%	N	%
Sex	Male						
	Female						
	Unknown						
Single/multiple birth	Single						
	Multiple						
Inborn/outborn birth	Inborn						
	Outborn						

Table 4 – Clinical history at baseline

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

Table 5 – Respiratory support at baseline

		Lower Oxygen Saturation		Higher Oxygen Saturation		Total	
		N	%	N	%	N	%
Continuous Positive Airway Pressure (CPAP)	No						
	Yes						
	Unknown						
Ventilation by endotracheal tube	No						
	Yes						
	Unknown						
Nasal cannulae	No						
	Yes						
	Unknown						

## 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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
Death or major disability <sup>^</sup> by 18-24 months corrected age						

<sup>^</sup> **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<sup>#</sup> by 18-24 months corrected age

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
Death or major disability <sup>#</sup> by 18-24 months corrected age						

<sup>#</sup> *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.

\* 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<sup>+</sup> by 18-24 months corrected age

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
Death or major disability <sup>+</sup> by 18-24 months corrected age						

<sup>+</sup> 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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
ROP treatment						

\* values adjusted for trials and multiple births

## 2.6.3 Measures of respiratory support

Table 10 – Respiratory support (binary outcomes)

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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)

	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted* Mean difference (95% CI)	p-value
	Median (IQR)	Median (IQR)		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Mean difference (95% CI)	p-value
	Mean ± SD		Mean ± SD			
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
	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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
	Major disability (as per protocol) <sup>^</sup> by 18-24 months corrected age					
Major disability (trialist defined) <sup>#</sup> by 18-24 months corrected age						

<sup>^</sup> 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.

<sup>#</sup> 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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
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

	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted* Mean Difference (95% CI)	p-value
	Mean ± SD	Mean ± SD		
Cognitive				
Language				
Receptive communication				
Expressive communication				

\* values adjusted for trials and multiple births

### 2.6.14 Death

Table 22 – Deaths

	Lower Oxygen Saturation		Higher Oxygen Saturation		Adjusted* Relative Risk (95% CI)	p-value
	N	%	N	%		
	Death prior to 18-24 months corrected age					
Death prior to 36 weeks postmenstrual age						
Death prior to discharge						

\* values adjusted for trials and multiple births

Table 23 – Median survival times

	Lower Oxygen Saturation	Higher Oxygen Saturation	Hazard ratio (95% CI)	p-value*
Median overall survival (months)				

\* Log-rank test

Figure 1 – Kaplan-Meier Overall Survival Curves

### 3 Abbreviations

<b>AE</b>	Adverse Event
<b>BOOST</b>	Benefits of Oxygen Saturation Targeting
<b>BPD</b>	Broncho-Pulmonary Dysplasia
<b>BSID</b>	Bayley Scales of Infant and Toddler Development
<b>CLD</b>	Chronic Lung Disease
<b>COT</b>	Canadian Oxygen Trial
<b>CPAP</b>	Continuous Positive Airway Pressure
<b>CRF</b>	Case Report Form
<b>GCP</b>	Good Clinical Practice
<b>GEE</b>	Generalised Estimating Equations
<b>GMDS</b>	Griffiths Mental Developmental Scales
<b>GMFCS</b>	Gross Motor Function Classification System
<b>HR</b>	Hazard Ratio
<b>IDSMC</b>	Independent Data and Safety Monitoring Committee
<b>IPD</b>	Individual participant data
<b>LLN</b>	Lower Limit of Normal Range
<b>MACS</b>	Manual Ability Classification System
<b>MDI</b>	Mental Development Index
<b>NEC</b>	Necrotising Enterocolitis
<b>NeOProm</b>	Neonatal Oxygenation Prospective Meta-Analysis
<b>NHMRC CTC</b>	National Health and Medical Research Council Clinical Trials Centre
<b>OS</b>	Overall Survival
<b>PDA</b>	Patent Ductus Arteriosus
<b>PDI</b>	Psychomotor Development Index
<b>PMA</b>	Prospective Meta-Analysis
<b>pma</b>	Postmenstrual age
<b>ROP</b>	Retinopathy of Prematurity
<b>RRR</b>	Relative Risk Reduction
<b>SAE</b>	Serious Adverse Event
<b>SD</b>	Standard Deviation
<b>SGS</b>	Schedule of Growing Skills
<b>SpO<sub>2</sub></b>	Oxygen Saturation
<b>SUPPORT</b>	Surfactant Positive Airway Pressure and Pulse Oximetry Trial
<b>ULN</b>	Upper Limit of Normal Range
<b>WPPSI</b>	Wechsler Preschool and Primary Scales of Intelligence
<b>95% CI</b>	95% Confidence Interval

---

## 4 References

1. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
  2. Bayley N. *Manual for the Bayley Scales of Infant Development*. (Third Edition) San Antonio, Texas: Psych Corp, 2006.
  3. Cole TJ, Statnikov Y, Santhakumaran S, Pan H, Modi N, Neonatal Data Analysis Unit and the Preterm Growth Investigator Group. Birth weight and longitudinal growth in infants born below 32 weeks' gestation: a UK population study. *Arch Dis Child Fetal Neonatal Ed* 2014; 99:F34-40.
  4. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatrica* 2006; Suppl 450: 76-85.
  5. Zou GY. A modified Poisson regression approach to prospective studies with binary data. *American Journal of Epidemiology* 2004; 159(7): 702-706.
  6. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. *Annual Review of Public Health* 2002; 23:151-169.
-

## Appendix A: List of tables and figures

Table 1 – Stratification variables .....	16
Table 2 – Participant characteristics (continuous variables) .....	18
Table 3 – Participant characteristics (categorical variables).....	19
Table 4 – Clinical history at baseline .....	19
Table 5 – Respiratory support at baseline .....	19
Table 6 – Primary outcome: death or major disability by 18-24 months corrected age.....	20
Table 7 – Primary outcome: death or major disability <sup>#</sup> by 18-24 months corrected age .....	20
Table 8 – Primary outcome: death or major disability <sup>+</sup> by 18-24 months corrected age .....	20
Table 9 – ROP treatment .....	21
Table 10 – Respiratory support (binary outcomes).....	21
Table 11 – Respiratory support (continuous outcomes) .....	21
Table 16 – Patent ductus arteriosus (PDA) diagnosed by ultrasound and requiring medical or surgical treatment .....	22
Table 13 – Patent ductus arteriosus (PDA) receiving surgical treatment.....	22
Table 14 – Necrotising enterocolitis (NEC) receiving surgery or leading to death .....	22
Table 15 – Weight z score .....	23
Table 16 – One or more re-admissions to hospital .....	23
Table 17 – Major disability by 18-24 months corrected age .....	23
Table 18 – Cerebral palsy.....	24
Table 19 – Severe visual impairment .....	24
Table 20 – Deafness requiring hearing aids.....	24
Table 21 – Quantitative Bayley-III scores .....	25
Table 22 – Deaths.....	25
Table 23 – Median survival times .....	25
Figure 1 – Kaplan-Meier Overall Survival Curves.....	25

---

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

Acronym	BOOST-II Australia	BOOST-II UK	BOOST-NZ	SUPPORT	COT
Registration #	ACTRN12605000055606	ISRCTN00842661	ACTRN12605000253606	NCT00233324	ISRCTN62491227
Sample size					
Planned	1200	1200	320	1310	1200
Actual	1135	973	340	1310	1201
Countries of recruitment	Australia	United Kingdom	New Zealand	United States of America	Canada, USA, Argentina, Germany, Israel, Finland, Norway
Participants	Infants < 28 wks gestation inborn or outborn < 24 hrs old	Infants < 28 wks gestation < 12 hrs old (24 hrs if outborn)	Infants < 28 wks gestation inborn or outborn < 24 hrs old	Infants 24-27 wks gestation, < 2 hrs old	Infants 23 0/7-27 6/7 wks gestation < 24 hrs old
Blinded?	Yes	Yes	Yes	Yes	Yes
Intervention	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)
Comparator	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)
Intervention & comparator duration	Oximeter applied after randomisation, asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO2 > 96% in room air for 95% of time over 3 days.	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.	Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO2 > 96% in room air for 95% of time over 3 days.	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.	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 &/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 &/or oxygen).

Primary outcome(s)	<p>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following:</p> <ul style="list-style-type: none"> <li>* cognitive or language score &lt;85 on BSID-3</li> <li>* severe visual loss</li> <li>* cerebral palsy with inability to walk at 2 yrs</li> <li>* deafness requiring hearing aids</li> </ul>	<p>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following:</p> <ul style="list-style-type: none"> <li>* cognitive or language score &lt;85 on BSID-3</li> <li>* severe visual loss</li> <li>* cerebral palsy with inability to walk at 2 yrs</li> <li>* deafness requiring (or too severe to benefit from) hearing aids</li> </ul>	<p>Death or survival with major disability at 2 yrs corrected for gestation. Major disability defined as having any of the following:</p> <ul style="list-style-type: none"> <li>* composite cognitive language score Bayley-III&lt;85 or MDI&lt;70 on the Bayley-II assessment.</li> <li>* severe visual loss</li> <li>* cerebral palsy defined as GMFCS level 2 or higher</li> <li>* deafness requiring hearing aids</li> </ul>	<p>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).</p>	<p>Death or survival with major disability at 18-21 months corrected for gestation. Major disability defined as having any of the following:</p> <ul style="list-style-type: none"> <li>* cognitive score &lt;85 and/or language score &lt;85 on BSID-3</li> <li>* severe visual loss</li> <li>* cerebral palsy with inability to crawl or walk independently</li> <li>* deafness requiring hearing aids</li> </ul>
--------------------	---	---	---	---	---

**Appendix C: Primary outcome of death or major disability at 18-24 months corrected age as defined by each trial and NeOProm Collaboration**

Acronym	NeOProm	BOOST-II Australia	BOOST-II UK	BOOST-NZ	SUPPORT	COT
Registration #	NCT01124331	ACTRN12605000055606	ISRCTN00842661	ACTRN12605000253606	NCT00233324	ISRCTN62491227
Death	At 18-24 months corrected age	At 24 months corrected age	At 24 months corrected age	At 24 months corrected age	At 24 months corrected age	At 18 months corrected age
Cognitive or language delay	Composite cognitive and/or language score <85 on Bayley-III	Composite cognitive language score Bayley-III<85 or MDI<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 <10 words; or language problems indicated on the short health assessment, delayed development by >12 months, other severe impairment.	Combined language or cognitive score of <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.	Composite cognitive language score Bayley-III<85 or MDI<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 <10 words; or language problems indicated on the short health assessment, delayed development by >12 months, other severe impairment.	Cognitive composite score on Bayley-III<70.	Composite cognitive and/or language score <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.
Gross motor	GMFCS level 2 or	GMFCS level 2 or higher,	Severe cerebral palsy	GMFCS level 2 or higher,	Moderate to severe	Level 2 or higher

disability	higher	as indicated on the health status or short health status assessments	(unable to walk without help at 2 years)	as indicated on the health status or short health status assessments	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.	according to GMFCS. Normal level is assigned if a child can walk 10 steps independently at 18 months
Severe hearing loss	Deafness requiring hearing aids	Requiring hearing aids, as indicated on the health status or short health status assessments	Deafness requiring (or too severe to benefit from) a hearing aid	Requiring hearing aids, as indicated on the health status or short health status assessments	The inability to understand oral directions of the examiner and to communicate, with or without hearing amplification	Prescribed hearing aids or cochlear implants
Severe visual impairment	Severe visual impairment as defined by trialists	Legal blindness, as indicated on the health status or short health status assessments	Severe visual loss certifiable as legally blind or partially sighted	Legal blindness, as indicated on the health status or short health status assessments	Vision worse than 20/200	Corrected visual acuity <20/200 in the better eye

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

Acronym	NeOProm	BOOST-II Australia	BOOST-II UK	BOOST-NZ	SUPPORT	COT
---------	---------	--------------------	-------------	----------	---------	-----



Registration #	NCT01124331	ACTRN12605000055606	ISRCTN00842661	ACTRN12605000253606	NCT00233324	ISRCTN62491227
Retinopathy of prematurity (ROP)	Retinopathy of prematurity (ROP) treatment by laser photocoagulation or cryotherapy or anti-VEGF injection	ROP stage $\geq 3$ subjected to retinal surgery	ROP stage $\geq 3$ or APROP	ROP stage $\geq 3$ subjected to retinal surgery	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	ROP stage $\geq 3$ . Severe retinopathy defined as unilateral or bilateral disease of stages 4 or 5 or receipt of retinal therapy in at least 1 eye
Measures of respiratory support	Supplemental oxygen requirement at 36 postmenstrual age; postmenstrual age ceased endotracheal intubation, continuous positive airway pressure (CPAP), supplemental oxygen, and home oxygen (if received)	Stop date recorded when used for $\geq 30$ minutes for endotracheal intubation, CPAP and supplemental oxygen. Last date of home oxygen use recorded.	Stop date not collected for endotracheal intubation or CPAP. Last date of home oxygen use recorded.	Last date recorded when used for $\geq 30$ minutes for endotracheal intubation, CPAP and supplemental oxygen. Last date of home oxygen use recorded.	Stop date not collected for endotracheal intubation, CPAP or supplemental oxygen use past 36 weeks gestational age.	Final stop date recorded for endotracheal intubation, CPAP and supplemental oxygen including use of supplemental oxygen or positive airway pressure at home.
PDA diagnosed by ultrasound and receiving any treatment	PDA diagnosed by ultrasound and receiving any treatment	PDA diagnosed by ultrasound	PDA diagnosed, but not necessarily by ultrasound	PDA diagnosed by ultrasound	PDA diagnosed, but not necessarily by ultrasound	Any diagnosis of PDA receiving therapy
PDA receiving surgical treatment	PDA diagnosed by ultrasound and receiving surgical treatment	PDA requiring surgical ligation	PDA requiring surgery	PDA requiring surgical ligation	PDA requiring surgery	PDA requiring surgical ligation
NEC requiring surgery or leading to death	NEC requiring surgery or leading to death	NEC requiring surgery or leading to death	NEC requiring surgery or leading to death	NEC requiring surgery or leading to death	Modified Bell's stage $\geq 2$ on a scale ranging from 1-3	Diagnosed during surgery or by a finding of pneumatosis intestinalis, hepatobiliary gas or free intraperitoneal air on XR
Cerebral palsy	Cerebral palsy with GMFCS level 2 or higher or MACS level 2 or higher at 18-24 months corrected age	Cerebral palsy with GMFCS score $\geq$ level 2	Unable to walk without help at 2 years (MACS level 1 or higher) and/or GMFCS score $\geq$ level 2	Cerebral palsy with GMFCS score $\geq$ level 2	Moderate to severe cerebral palsy defined as a non-progressive disorder with abnormal muscle tone in at least one arm or leg that was	Level 2 or higher according to GMFCS. Normal level is assigned if a child can walk 10 steps independently at 18 months

					associated with abnormal control of movement or posture and a GMFCS score $\geq 2$	
Weight z-score	Weight measured in grams, z-score calculated using UK or WHO percentile charts, accounting for corrected age and gender	Weight measured in grams	Weight measured in grams	Weight measured in grams	Weight measured in grams	Weight measured in grams
Re-admissions to hospital	One or more re-admissions to hospital up to 18-24 months corrected age	Re-admissions to hospital at 2 years corrected age	Re-admissions to hospital until 2 years after delivery was due (and cause)	Re-admissions to hospital at 2 years corrected age	Re-admissions to hospital at 2 years corrected age	Re-admission to hospital - available for children whose family provided a standardised medical history at 18 months