



NHMRC Clinical Trials Centre



Which oxygen saturation level should we use for very premature infants? A randomised controlled trial

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STUDY ORGANISATION

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Trial Management Committee

The core members of Trial Management Committee are listed below. Additional members may be invited to Trial Management Committee meetings.

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Colin Morley	Professor of Neonatal Medicine, The University of Melbourne, The Royal Women's Hospital and The Royal Children's Hospital
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Val Gebski	Associate Professor, Head, Biostatistics & Research Methodology, The University of Sydney

Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will be appointed by the Trial Management Committee and will be independent of the study organisation. It will regularly review the outcome and safety data provided by the NHMRC CTC, reporting to the Trial Management Committee.

SYNOPSIS

OBJECTIVE

To investigate the effect of two different oxygen saturation levels within the range of common clinical practice on the health of very premature infants.

STUDY DESIGN

Multi-centre, double masked, randomised controlled trial.

ELIGIBILITY

INCLUSIONS: Infants are eligible if -

1. They are 27⁶ weeks gestation or less
2. They are less than 24 hours old
3. Parental consent is obtained

EXCLUSIONS: Infants are ineligible if –

1. There is a congenital anomaly affecting oxygenation or long term development.
2. Death is imminent.
2. Two years follow-up is judged unlikely

ENDPOINTS

Primary Outcome

- Death or major disability at 2 years old corrected for gestation at birth.
Major disability is defined as having any of the following:
 - MDI less than 70 on Bayley Scales of Infant Development III
 - severe visual loss (cannot fixate or is legally blind)
 - cerebral palsy with inability to walk at 2 years corrected gestational age
 - deafness requiring hearing aids

Secondary Outcomes

Retinopathy of prematurity (ROP), duration of oxygen therapy, duration of respiratory support, PDA, proven infection, NEC, chronic lung disease (CLD)(treated with oxygen at 36 weeks gestational age), growth, re-admissions to hospital up to 2 years old, cerebral palsy and unable to walk at 2 years corrected gestational age, blindness (<6/60 vision), deaf using hearing aid, mean MDI and PDI scores on Bayley Scales <70, death from pulmonary causes before discharge from hospital.

RANDOMISATION

By telephone, using a computerised interactive voice response system (IVRS).

After the study oximeter is allocated, **staff will (a) target oxygen saturation (SpO₂) 88 – 92% and (b) aim to maximize time spent with SpO₂ between 85 - 95%.**

Only a specially adjusted, masked Masimo Radical SET study oximeter with a $\pm 3\%$ offset is used until the baby is 36 weeks corrected gestational age.. No other oximeter is attached to the baby at the same time as the study oximeter (barring exceptional circumstances).

- From 85-95%, the offset will be 3% above or below actual SpO₂.
- Outside 85-95%, study oximeters read actual SpO₂.

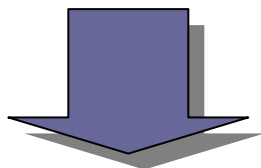
Each NICU is encouraged to adopt a uniform oxygen targeting policy for all infants , including those not recruited to BOOST II.

SAMPLE SIZE & POWER

A sample of 1200 infants has 80% power ($2p = 0.05$) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years (from 37% to 45% or from 37% to 29%). This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.

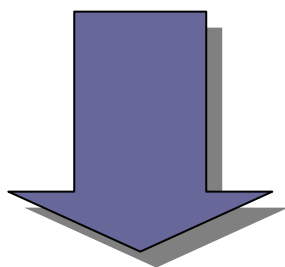
FLOW CHART

Eligibility



- **ALL** infants < 28⁰ weeks gestation – inborn or outborn
- Parental consent before or after birth
- Less than 24 hours old
- Infants are ineligible if they have any anomaly which may affect oxygenation or development, or death is imminent

Randomisation



while on supplementary oxygen

**Target SpO₂
88 – 92%**

**Minimize the time spent between
97-100%**

Recommended alarm limits:

Upper 94%

Lower 86%

[or between 80- 85%]

When baby is in NICU, complete Randomisation Sheet, Freephone 1800 – 821 855 then follow the voice prompts:

Please have these details written down on the Randomisation Sheet –

- *Hospital Number of mother*
- *Is there a congenital anomaly affecting oxygenation, [e.g., cyanotic heart disease, diaphragmatic hernia, hypoplastic lung, Potters syndrome] or affecting development [e.g. Down syndrome]?*

If YES, not eligible

- *Has parental consent been obtained?*

If NO, not eligible

- *Date of birth, time of birth*
- *Gestation*
- *Inborn or outborn*
- *Sex*

Study oximeter number and the Baby study number are now allocated

Always

- **Keep upper alarm at 94% if baby in supplementary oxygen.**
Only switch it off when in air.
- **Keep SpO₂ chart up to date**
- **Aim for ZERO time at SpO₂ 97 – 100% while on supplementary oxygen.**
[This reduces the risk of ROP and chronic lung disease]

No other work for neonatal staff

Research Nurse completes data collection at different time points

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1.0 STUDY SUMMARY

It is universally accepted that supplemental oxygen can be lifesaving in newborn infants with respiratory illness. However, the optimum range of oxygen saturation for preterm infants in the first few weeks from birth is unknown. A meta-analysis of trials of restricted versus liberal ambient oxygen concentrations since 1952¹ showed that restricting oxygen reduced retinal damage and risk of blindness. However, the trials could not exclude important differences in mortality, chronic lung disease, or long term growth, neuro-development, lung or visual function.

Aims:

The Australian BOOST II study is a double masked randomised controlled trial (RCT) of 1200 infants of 27⁶ weeks gestation or less. It will test whether varying inspired oxygen concentration so as to target the lower (85-89%) versus the higher end (91-95%) of a range of arterial oxygen saturation (SpO₂) in common use worldwide (85 – 95%), from the day of birth until 36 weeks corrected gestational age, reduces severe retinopathy of prematurity (ROP), chronic lung disease, poor growth and the use of health service resources, with no clinically significant change in the combined outcome of mortality or major disability at 2 years of age.

Methods:

Infants who are born at 27⁶ weeks gestation or less are randomly assigned within 24 hours of birth to lower or higher targeted SpO₂ until 36 weeks corrected gestational age. SpO₂ is measured with masked Masimo Radical SET oximeters. Study oximeters will be offset by about $\pm 3\%$ for values of SpO₂ between 85 and 95%. Outside those values, oximeters read actual SpO₂. **Whenever the baby is on supplementary oxygen, staff will be asked (a) to target 88-92% and (b) to keep the time spent between 96-100% as close to zero as possible**, for as long as the study oximeter remains on the baby. In half the oximeters, 88-92% will represent actual values of about 85 to 89% and in the other half it will represent actual values of about 91 to 95%. Alarm limits while in supplementary oxygen will be set according to local policy, but ***an upper alarm of 94% and a lower alarm of 86% are recommended.***

Power:

A trial with 1200 infants has more than 80% power (2p = 0.05) to exclude an 8% absolute difference in death or major disability at 2 years (the primary outcome for the trial) and to detect absolute differences in severe ROP of 2.2% points, from 10% to 7.8%, and in chronic lung disease of 8% points, from 40% to 32%.

Education:

Education and acceptance of the goals of the study by all caregivers is a major priority. Historically, there are reports that some staff in trials in the 1950s actually increased FiO₂ surreptitiously to 100% in infants who had been allocated restricted oxygen, as they wished to prevent hypoxia and did not appreciate the potential risks of too much oxygen.

The success of BOOST II and other oxygen trials will depend on the wholehearted commitment of nursing and medical staff at the bedside and of senior clinicians. Good compliance with the SpO₂ target of 88-92% and in the range 85-95% is essential for adequate separation of the study arms, as there is no difference between the values displayed by the study oximeters outside that range. This goal can be achieved by minimizing the time spent with SpO₂ at 96-100% or below 85%.

Significance:

After more than half a century of uncertainty, this study will help define the optimum oxygen saturation, and may help to reduce iatrogenic oxygen injury, in many thousands of very preterm babies worldwide.

2.0 BACKGROUND

A healthy start for premature infants

Each year, about 850 children born at 27⁶ weeks gestation or less are admitted to neonatal intensive care units (NICUs) in Australia and about 75% are discharged home alive.² Despite nearly normal life expectancy many survivors sustain severe morbidity.³ Their risk of chronic lung disease, poor growth, respiratory illness, hospital re-admissions, visual deficits, cerebral palsy, sensori-neural disability and cognitive, educational and behavioural impairment is higher than in term infants.⁴ They account for much of the costs and disability from NICU care.⁵ Their risk of visual deficit may be increasing.⁶ Reducing these morbidities would enhance their quality of life and benefit their family and the community.⁷

Oxygen toxicity in very premature infants

Oxygen is a very common therapy for very premature infants. It has been associated with significant improvements in neonatal survival and disability.⁸ However, these infants are highly sensitive to its harmful biochemical and physiological effects. While oxygen is essential for metabolism, its by-products – free radicals and reactive oxygen species – cause tissue injury. Toxic oxygen radicals are increased in hyperoxaemia (arterial oxygen too high)⁹ and in re-oxygenation after hypoxaemia (arterial oxygen too low). Premature infants are vulnerable to oxidative stress because they lack antioxidant protection.⁹ They lack plasma radical scavengers, such as Vitamin E or beta-carotene, antioxidant enzymes, such as glutathione peroxidase, and their red cells lack superoxide dismutase.

Hyperoxaemia can constrict or obliterate vessels in an immature eye and brain, causing ischaemic injury.⁹ Exposure to less oxygen is a simple, logical strategy that could reduce oxidative stress and tissue injury and prevent morbidity in very premature infants. In healthy premature infants breathing air, arterial oxygen saturation is 85 – 98%. However, the optimum range of arterial oxygen to minimise organ damage, without causing hypoxic injury, is unknown.

How oxygen causes Retinopathy of Prematurity (ROP)

In early fetal life, the retina is avascular. Vessels grow out from the centre, controlled by vascular endothelial growth factor (VEGF), released by normal hypoxic retinal tissue. After premature birth, treatment with inspired oxygen may flood the retina with oxygen. As lung disease resolves and inspired oxygen is reduced, the ischaemic peripheral retina becomes severely hypoxic. There is abnormally high secretion of VEGF and new vessels and fibrous tissue proliferate and invade the vitreous. Fibrous contraction leads to retinal detachment and visual loss.¹⁰ Destroying these proliferating vessels by ablative laser surgery can prevent retinal detachment. This saves central vision in some cases, but there is often residual visual loss. Of survivors at 27⁶ weeks gestation or less, **50% have ROP, 12.5% have severe (Grade III/ IV) ROP,² 56% of these have surgery, but about 10% of those treated become blind.** New recommendations will result in more infants with severe ROP having laser surgery.¹⁰ Of survivors of 28-29 weeks' gestation, <2% get severe ROP.²

Oxygen and lung disease

High inspired oxygen contributes to chronic lung disease (CLD), also known as broncho pulmonary dysplasia (BPD), which is associated with poor respiratory and neurodevelopmental outcomes.^{12,13} Improved survival has increased chronic lung disease, leading to poor growth, impaired neuro-development and greater health costs.

Oxygen and brain injury

As with any treatment, oxygen might increase disability by salvaging sick babies who would otherwise have died.⁸ Oxygen may also directly contribute to brain damage in premature infants, through oxidative stress and low cerebral blood flow. Oxidative damage to pre-myelinating oligodendrocytes in cerebral white matter is proposed as a mechanism of periventricular leukomalacia¹⁴ - a form of white matter damage correlated with cerebral palsy. In premature infants, hyperoxia reduces cerebral blood flow velocity independently of the effects of hypocapnia or hypotension.¹⁵

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These mechanisms may explain why hyperoxaemia was a risk factor for cerebral palsy in a study of 1105 preterm infants.¹⁶ Hyperoxaemia in the first eight days was associated with twice the odds of cerebral palsy at 2 years, after adjusting for other variables. The adjusted odds of cerebral palsy increased eightfold for infants with the highest versus the lowest quintiles of exposure to hyperoxaemia, indicating a dose-response effect. Importantly, hyperoxaemia was defined as arterial oxygen above 60 mm Hg, in contrast with the long accepted upper limit of 80 mm Hg.^{17, 18}

Results of previous trials of restricted or targeted oxygen in very premature infants

In a 2004 editorial in *Pediatrics*,¹⁹ Dr William Silverman, formerly of Columbia University, states,

“...there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants. For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP-blindness, chronic lung disease and brain damage) was, and remains to this day, unknown.”

The first case of ROP (originally called Retrolental Fibroplasia) was reported in 1942. By 1954, ROP had blinded about 10,000 infants.^{19,20} In 1954-56, 3 RCTs enrolling 341 infants proved that breathing unrestricted concentrations of inspired oxygen was a major cause of ROP.¹ Arterial oxygen levels were not measured, so the concentration of inspired oxygen could not be targeted to meet each baby's needs. To prevent ROP, all premature infants were restricted to breathing less than 40% inspired oxygen. The epidemic of blindness stopped – but, perhaps, at heavy cost. In the next 20 years over 150,000 premature babies are thought to have died of hypoxic respiratory failure.²¹⁻²³ For every infant whose sight was saved, it is estimated that 16 may have died^{19, 21-23} and many others may have developed spastic diplegia.²⁴ This might have been avoided had a larger RCT determined if oxygen restriction from birth increased or decreased death and disability.

The STOP ROP trial: The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity trial used pulse oximetry to target lower (89-94%) or higher (96-99%) arterial oxygen saturation (SpO₂)²⁵ in 649 premature infants with early ROP. The higher range caused more adverse respiratory events, including pneumonia, chronic lung disease requiring oxygen and diuretic therapy.

The first BOOST Study: The Australian Benefits of Oxygen Saturation Targeting RCT [BOOST] was reported in the *New England Journal of Medicine*.²⁶ It randomly assigned 358 infants <30 weeks' gestation, from ≥ 3 weeks after birth until they breathed air, to target oxygen saturation (SpO₂) of 91-94% or 95-98%. The study aimed to decide if targeting higher SpO₂ improved growth and development. It did not, but higher SpO₂ did increase days of oxygen therapy and use of health care resources. Masked, adjusted oximeters were a major innovation. Half were adjusted to display masked values 2% lower than actual SpO₂, the others displayed masked values 2% higher. Staff were unaware of actual SpO₂ and targeted a masked range of 93-96%. Masked oximetry was safe and acceptable to staff and parents. It was concluded that RCTs are needed to determine how different SpO₂ levels from the day of birth affect ROP, chronic lung disease, growth, disability and mortality.^{19, 26}

Current guidelines for levels of arterial oxygen to minimise the risk of ROP

A cohort study in 1977 was unable to establish a relationship between arterial oxygen tension and retinopathy.²⁷ A range of 50–80 mm Hg became widely accepted,^{17, 18, 28} but based on consensus rather than fact. A later study confirmed that ROP occurred more often with arterial oxygen tension above 80 mm Hg²⁹ but did not determine if another limit was safer. Oximeters measuring functional SpO₂ display values about 2% higher than fractional SpO₂. The 95% confidence interval for normal fetal umbilical venous oxygen tension is about 20 – 60 mm Hg, decreasing with increasing gestational age.^{30,31} This is equivalent to a range of oxygen saturation of about 60 – 90%. In transposing oxygen tensions of 50–80 mm Hg into arterial oxygen saturation, most clinicians have targeted functional SpO₂ 90–95%.³²

Four recent cohort studies of lower oxygen saturation targets in relation to short-term outcome

1. Tin showed that lower SpO₂ correlated with improved outcomes in infants <28 weeks' gestation.³³ Alarm limits for SpO₂ in four NICUs ranged from 70–90% to 88–98%. Babies in the NICU targeting SpO₂

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70-90% had less ROP surgery than those in the NICU targeting SpO₂ 88-98% (6.2% v 27.2%: 80% relative risk reduction (RRR), p < 0.01). Survivors were ventilated for shorter periods (13.9 v 31.4 days), fewer needed oxygen at 36 weeks' postmenstrual age (18% v 46 % (61% RRR), and fewer were below the 3rd centile for weight at discharge (17% v 45%, 62% RRR) (all p< 0.01) while survival (52% v 53%) and cerebral palsy (15% v 17%) at one year were similar.³³

2. Anderson reported less Stage III/ IV ROP (2.4% vs. 5.5%, p<0.001) and less ROP surgery (1.3% v. 3.3%, 61% RRR, p<0.037) in NICUs with functional SpO₂ upper limit ≤ 92% vs >92%.³⁴

3. Sun studied 1544 infants weighing <1000 g in NICUs with upper limit SpO₂ of ≤95% vs >95%. NICUs with ≤95% limits had less Stage III ROP (10% vs 29%), surgery (4% vs 12 %, 67% RRR), chronic lung disease (27% vs 53%, 49% RRR) (all P< 0.001) and similar mortality (17% v 24%).³⁵

4. Chow³⁶ found that 83-90% functional SpO₂ was associated with less Stage III-IV ROP than 90 – 98% in historical controls. From 1998 to 2001, it fell from 12.5% to 2.5% (80% RRR, p= 0.01) and ROP surgery fell from 7.5% (6/80) to zero (0/188) (100% RRR, p=0.0006). Fewer infants had Stage III/ IV ROP than in the Vermont Oxford Quality Improvement Network (VON).

Less inspired oxygen (to target SpO₂ <90%) may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development.^{37,38} More inspired oxygen (to target SpO₂ >90%) may increase severe ROP and chronic lung disease and impair survival and neuro-development.^{16,33-36} After recent studies,³³⁻³⁶ more NICUs are adopting lower SpO₂. This trend may increase before the risks and benefits are determined. The disastrous mistakes of the 1950s¹⁹⁻²⁴ show how rapidly opinions can shift, destroying the chance of reliable evidence.

Determination of net clinical benefit or harm

Because different oxygen targets may have competing risks, it is essential that trials are allowed to accumulate sufficiently large numbers to be able to demonstrate net clinical benefit or harm. Members of the POST ROP Planning Group have pointed out that, while several hundred patients may be sufficient to demonstrate important differences in severe ROP, a much larger sample of some thousands could well be necessary to exclude small, important differences in outcome such as mortality and disability.³⁹ For example, a 5% or 6% absolute difference in an outcome of death or cerebral palsy is “small” but would have major implications for public health.

“Evidence of net benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment because of a 3% reduction in severe ROP in the lower oxygen group before the trial had accumulated sufficient power to exclude a 6% increase in mortality or severe neuro-developmental impairment in the same group. In this case, if the trial were terminated prematurely and lower oxygen became the clinical standard, for every infant whose sight was saved, 2 would die or survive with major disability.”³⁹

Determining the terms of reference of the Data and Safety Monitoring Committee (DSMC):

An early meeting of the independent Data and Safety Monitoring Committee (DSMC) will be held with the Trial Management Committee (TMC) to discuss the roles and responsibilities of the DSMC and agree terms of reference.³⁹⁻⁴⁴ Among the issues to be addressed are:

- i) the need to assess net clinical benefit or harm³⁹ as data accumulate in this or similar trials;
- ii) whether it is appropriate to specify futility as a criterion for recommending early closure⁴⁴
- iii) the potential for an inappropriate recommendation of early closure that may arise from having multiple safety events (or harms) versus a single primary outcome (or benefit) of disability-free survival.^{45,46}
- iv) the need for any surrogate outcome to fulfil stringent, pre-specified criteria, to be valid.^{47,48}

3.0 TRIAL OBJECTIVES AND PURPOSE

The aim of the study is to determine whether there is any difference in outcome at two years when infants born at 27⁶ weeks gestation or less have their oxygen saturation targeted between 91 and 95% compared with 85 to 89%.

The primary question is 'Does this oxygen saturation difference increase or decrease the composite outcome of death and major disability by 8% or more?'

BOOST II is a randomised trial of this primary outcome, with power to detect important risks or benefits in potentially conflicting secondary outcomes.

4.0 TRIAL DESIGN

4.1 Design

This is a multi-centre, double-masked, randomised controlled clinical trial.

4.2 Randomisation

Randomisation will be performed centrally by telephone. It will be stratified by site, sex, gestation (<26, ≥26 weeks), single or multiple birth and inborn or outborn. The computer-generated randomisation lists will be prepared by an independent statistician at the NHMRC Clinical Trials Centre, The University of Sydney. The randomisation code will be securely held by the statistical group at the coordinating centre and will not be accessible to staff involved in the baby's daily clinical care.

4.3 Endpoints

Primary outcome

Death or survival with major disability at 2 years corrected for gestation.

Major disability is defined as having any of the following:

- Cognition: Bayley, Mental Development Index MDI<70; (- 2SD)
- Neuromotor function: signs of cerebral palsy with inability to walk unassisted at 2 years corrected for gestation.
- Severe visual loss: cannot fixate or is legally blind; corrected visual acuity < 6/60 in both eyes
- Hearing deficit: diagnosis of deafness requiring hearing aid, or cochlear implants

Secondary outcomes

- Severe ROP subjected to retinal surgery¹¹
- Respiratory morbidity: Quantitative comparisons of total duration of respiratory support (duration of oxygen therapy, defined as (a) oxygen at 36 weeks postmenstrual age, (b) days of endotracheal intubation (c) days of continuous positive airway pressure (CPAP), (d) days of oxygen, (e) days on home oxygen)
- Patent ductus arteriosus (PDA) diagnosed by ultrasound and requiring medical or surgical treatment
- Necrotizing enterocolitis (NEC) requiring surgery.
- Proven infection
- Growth: weight, head circumference, length (birth, discharge, and at 2 years corrected for gestation).
- Retinal structure: at 12 months post menstrual age or when last examined.
- Readmission to hospital up to 2 years corrected for gestation.
- Any respiratory illnesses.
- Mean MDI and Psychomotor Development Index (PDI) scores
- Death from pulmonary causes before hospital discharge

5.0 SUBJECT POPULATION

5.1 Subject Population

Infants born at ≥ 27 weeks gestation or less and less than 24 hours old.

5.2 Inclusion criteria

A baby is eligible if

- a) born at ≥ 27 weeks gestation or less (in-born or out-born)
- b) less than 24 hours of age
- c) there is informed consent by parent(s) or legal guardian

5.3 Exclusion criteria

A baby is not eligible if

- a) there is a known congenital anomaly that could affect oxygenation or development
- b) death is imminent
- c) attendance for follow-up for 2 years is judged unlikely

5.4 Withdrawal of parental consent

The parent can decide to withdraw their baby from the study at any time. Full details of the reasons for withdrawal, if given, should be recorded on the Case Record Form (CRF). If the parents choose to withdraw their infant from the trial during the intervention phase, permission will be sought to follow the baby's progress up to a minimum of 2 years. Parents may choose to withdraw this permission as well.

If the parent withdraws consent for their baby to participate in the study this will not affect the baby's medical treatment or relationship with the medical staff at the hospital. The baby's care should be continued according to the hospital neonatal unit's current guidelines.

6.0 TREATMENT

6.1 Study Intervention

The intervention is random assignment of study oximeters to target SpO₂ 85-89% or 91-95%. The assigned SpO₂ ranges are masked. The study oximeter is the only oximeter with which the baby will be monitored until the study intervention is completed. *

Masked Study Oximeters

Oxygen saturation is measured with adjusted, masked Masimo Radical SET pulse oximeters measuring functional SpO₂. Like all types of pulse oximeters, these estimate SpO₂ with one standard deviation of about 3%. Masking is achieved by offsetting the two assigned SpO₂ ranges by $\pm 3\%$ points. The target for the displayed range is 88-92% for both study groups. The masked ranges (SpO₂ 85-89% and SpO₂ 91-95%) are consistent with a range of SpO₂ values (85-95%) in current use in many neonatal units.

The displayed SpO₂ is about 3% higher or about 3% lower than the assigned range.

- o If assigned to SpO₂ 85-89% \Rightarrow offset is about +3% \Rightarrow displayed SpO₂ = 88-92%.
- o If assigned to SpO₂ 91-95% \Rightarrow offset is about -3% \Rightarrow displayed SpO₂ = 88-92%.

To achieve good compliance the recommended setting of the alarm limits are as follows-

- o the upper alarm limit at 94%
- o the lower alarm at 86% (or between 80 and 85%)

* Apart from exceptional circumstances as mentioned on page 12 in 'Methods for protecting against sources of bias'

If a baby is deemed to need oxygen saturation levels of 96-100% for any reason, such as surgery, this can be achieved without changing the study oximeter, as it reads the true, unadjusted value above 95%. The alarm setting must only be changed on a doctor's written orders.

Onset of intervention

Randomisation of the study oximeter will occur as soon as possible after admission to the NICU.

Duration of study intervention

Enrolled infants will be required to use the allocated trial oximeter for a minimum of two weeks, even if not requiring supplemental oxygen. The allocated oximeter will be used until the infant reaches a corrected gestational age of 36 weeks, or until the infant has a SpO₂ > 96% in room air for >95% of the time over 3 days. The frequency of monitoring the SpO₂ (continuous or intermittent), and the criteria for changing the FiO₂ or for stopping oxygen therapy are determined by the attending clinicians. Self-compliance will be monitored by the nurse at the cotside..

Methods for protecting against sources of bias

Investigators, clinical staff, families and those who assess outcome are all masked to randomisation, and study intervention. To prevent unmasking of study oximeters, the transition from displaying offset to actual values occurs incrementally over several seconds, showing all intermediate 'gap' values between 88-85%, or 93-96%.

There should never be a need to withdraw a study oximeter because a baby can be managed at 96-100% on the oximeter if clinically indicated. There should never be a need to unmask a study oximeter because a doctor or patient has the option to withdraw the study oximeter, if there were any specific concerns.

Rarely, it may be deemed necessary to evaluate right to left shunting across the ductus arteriosus by temporarily attaching two standard oximeters pre- and post-ductally. To avoid unmasking the study oximeter, this should be removed 5 minutes before attaching the standard oximeters. These should, in turn, be removed 5 minutes before re-attaching the study oximeter.

Any questions about withdrawing or unmasking a study oximeter should be directed to the coordinating centre.

6.2 Supply and Accountability of Study Oximeters

Masimo Corporation will ship oximeters to the Coordinating Centre who will be responsible for managing their distribution and tracking.

Study oximeters are prominently labeled to avoid inadvertent use on a non-study baby.

Study oximeters are to be used only on babies randomised to BOOST II.

Neonatal staff must stop using a standard oximeter at least 5 minutes before attaching the study oximeter.

Once assigned the study oximeter must be the only oximeter used on that infant until an oximeter is not needed, barring exceptional circumstances (see 6.1). **TO AVOID UNMASKING, NO OTHER OXIMETER MUST BE USED AT THE SAME TIME.**

Study personnel will be fully trained regarding proper procedures for use of study oximeters.

The Principal Investigator or the designated personnel at all sites will be responsible for the maintenance of logs to track the deployment of study oximeters. These logs must be available for audit by the NHMRC Clinical Trials Centre and regulatory agencies if required.

Oximeter sensors will be supplied by the local NICU.

6.3 Concurrent Trials

Participation in concurrent trials is permitted.

6.4 Assessment of oxygen saturation levels achieved

The following will be recorded:

1. Total time on oximeter (date/time started, date stopped, dates restarted/stopped if gap > 24 hrs)
2. Reason/s why use of oximeter was discontinued, temporarily or permanently.
3. Any decision to administer oxygen outside the study SpO₂ target range
4. Whether the baby is being transferred to another hospital with the study oximeter

6.5 Assessment of Two Year Outcome

Paediatricians and psychologists who are unaware of the child's oxygen target will assess all survivors at 2 years adjusted for prematurity. The paediatrician will determine outcomes such as cerebral palsy, defined as loss of motor function in association with abnormal muscle tone or power, and will reassess vision and hearing. All survivors will already have been screened for vision and hearing loss and these results will be recorded. An ophthalmologist or audiologist, as required, will reassess any child if doubts about vision or hearing persist at two years old. Data on hospital re-admissions will be confirmed from the source, with the parents' permission. Weight, length and head circumference will be measured and Z-scores calculated. The psychological assessment will include the Mental Developmental Index and the Psychomotor Developmental Index on the Bayley Scales of Infant Development - 3rd Edition (Bayley-III).

7.0 SAFETY

7.1 Assessment of Safety

The standard definition of a Serious Adverse Event (SAE) is any untoward medical occurrence that:

- results in death or
- is life-threatening or
- requires inpatient hospitalisation or prolongation of existing hospitalisation or
- results in persistent or significant disability/incapacity or
- other important medical events (such as requiring surgery) which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

Most of these events are common in very preterm infants, however, the proportion of unexpected serious adverse events (in the opinion of the investigator) is expected to be small. Unexpected SAEs are to be recorded and reported. They will be notified to the coordinating centre within one working day of the event becoming known to the Local Investigator.

The NHMRC Clinical Trials Centre will activate a notification cascade, which includes notifying the University of Sydney Ethics committee, Data and Safety Monitoring Committee, Trial Management Committee, and all other Principal Investigators participating in the study.

NHMRC Clinical Trials Centre will also notify the Therapeutic Goods and Administration (TGA) of reportable unexpected serious adverse events as specified in TGA regulations. The Investigator or delegate at each participating institution is responsible for reporting unexpected serious adverse events to their HREC, and may require a change to the Patient Information Sheet and Consent Form, with the coordinating centre informed of any changes. Unexpected serious adverse events will be monitored by the Data and Safety Monitoring Committee at least on an annual basis.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size

1200 babies are to be recruited from all over Australia. The group allocated high oxygen are expected to have a 37% rate of the primary combined outcome of mortality (13% mortality rate, excluding first day deaths²) and major disability (24% major disability rate^{5,49}) at two years; and a 10% rate of ROP surgery.^{2,11} This yields >80% power at 2p=0.05 to exclude an absolute risk difference (increase or decrease) of 8% points or more in primary outcome, from 37% to 45%, or 37% to 29% [22% relative risk

difference]. It gives >90% power to show an absolute risk reduction of 5% points or more in ROP surgery, from 10% to 5% [50% Relative Risk Ratio (RRR)] and in chronic lung disease from 40% to 32% [18% RRR]. While these are large differences, they match hypotheses from studies that link less oxygen with RRRs of 50-100% in ROP surgery and chronic lung disease or ventilator dependence.³³⁻³⁶

8.2 Statistical Analysis

The primary analysis of this pragmatic trial will be by intention to treat and will compare the composite of mortality and major disability at 24 months corrected for gestational age for all infants recruited. For secondary outcomes, adverse outcomes and protocol violations, analyses will be performed on all babies according to assigned treatment (intention-to-treat). Effect sizes and 95% confidence intervals will be presented for primary and secondary outcomes. For continuous factors, differences in means and for dichotomous and categorical factors, odds ratios and risk differences will be presented. Multi-variate comparisons including logistic and linear regressions and, if appropriate, proportional hazards (Cox) regression will also be used to explore the impact of major prognostic variables on outcome.

8.3 Economic analysis

The economic analysis will compare estimates, in and beyond the study, of the incremental effects of less oxygen on 3 outcomes, survival, life years and quality adjusted life years, relative to its incremental effects on resource use and treatment costs. If the incremental costs and effects of less oxygen are positive, (i.e. it increases both costs and health gain) its incremental cost effectiveness ratio (ICER) will be estimated as additional \$ spent per life, per life year and per Quality Adjusted Life Year (QALY) gained. If its incremental costs and effects are both negative, the ICER of less oxygen will be estimated as additional \$ saved per life, per life year and per QALY lost.⁵⁰ Other scenarios are that less oxygen is dominant (e.g. cost saving and more effective) or is dominated by high oxygen.

The methods for the economic evaluation of neonatal intensive care follow those employed previously in Australia, but with increased focus on secondary outcomes and better data on hospital re-admissions and non-ambulatory health care.³ Costs of initial NICU care will be estimated according to number of patient-days of respiratory support with mechanical ventilator or CPAP³ and estimates of costs of surgery for ROP based on micro-costing in a sub-study of these patients. Hospital admissions between discharge and 2 years of age will be assigned by diagnostic related group (DRG) and costed according to AN-DRG cost weights. Medicare Australia data will be requested (with prior parental consent), to estimate out-of-hospital resource use and costs, up to 2 years of age.

To estimate QALYs saved, utility weights will be assigned as 0 for dead, 0.4 for severe disability, 0.6 for moderate disability, 0.8 for mild disability and 1 for no disability.³ Utilities at 2 years will be aggregated for each group and divided by the number of children to calculate quality adjusted survival rates at 2 years. To estimate incremental life years beyond the study, life expectancy at 2 years is assumed to be 70 years, except for severely disabled children in whom it is assumed as 40 years.

If there are significant differences between trial arms in disability, lifetime costs of care will be estimated with a baseline of \$50,000 (\$A 1997) per year, varied in sensitivity analyses to reflect differences in Australian estimates of cost of treating disability by severity.⁵¹ If no differences in primary outcomes are observed, a cost minimisation analysis will be performed. To assess the robustness of conclusions, sensitivity analyses around baseline estimates of ICERs will be undertaken using 95% confidence intervals for treatment effects with varying assumptions about costs of hospital care, disability, utilities and life expectancy.

8.4 Prospective Meta- Analysis of randomised controlled trials of neonatal oxygen targeting

Meta-analysis of multiple randomised controlled trials increases the overall sample size and power to demonstrate treatment effects. However, if meta-analysis is performed when results of trials are known, data-dependent selection bias can occur. Trials with certain results can be deliberately included or excluded to manipulate the conclusions. A prospective meta-analysis (PMA) is a meta-analysis where randomised controlled trials are identified, evaluated and determined to be eligible before the results of any of them become known^{52,53}. PMA can therefore help to overcome some of the problems of retrospective meta-analyses. It enables: hypotheses to be specified a priori ignorant of the results of individual trials; prospective

application of selection criteria; and a priori statements of intended analyses, including sub-group analyses, to be made before the results of individual trials are known. This avoids potentially biased, data dependent emphasis on particular subgroups. In addition, pooling of individual patient data allows more informative subgroup analyses to be conducted. PMA provides the methodological advantages of a single 'mega-trial' while allowing greater practical flexibility. Thus collaborators can seek funding from different national agencies, spreading the financial burden, and can agree pre-specified differences in protocol, such as the precise timing of follow up or the lower limits of separation in the offsets of study oximeters.

The Australian BOOST II trial will contribute to a proposed PMA of neonatal oxygen trials with similar SpO₂ targets, protocols and outcomes. This PMA will be coordinated by Dr Lisa Askie of the Centre for Perinatal Health Services Research at the University of Sydney, supported by Professor John Simes, Professor David Henderson Smart, Associate Professor Val GebSKI and the Principal Investigators (or their nominated alternate) of potentially contributing RCTs, including the US NICHD SUPPORT Trial (Dr Neil Finer), US POST (Dr Cynthia Cole), BOOST II NZ (Dr Brian Darlow), BOOST II UK (Dr Edmund Hey) and the Canadian Oxygen Trial (COT) (Dr Barbara Schmidt).

9.0 STUDY STRUCTURE

9.1 CTC Coordinating Centre

The NHMRC Clinical Trials Coordinating Centre at the University of Sydney is the coordinating office for the BOOST II trial. The CTC is responsible for coordination of all aspects of the study in Australia, including performing the central randomisations, site management and monitoring, data collection,, statistical analyses and provide regular reports to the Data and Safety Monitoring Committee (DSMC).

9.2 Trial Management Committee

The Trial Management Committee (TMC) has overall responsibility for the design and conduct of the BOOST II study. This committee will meet regularly to discuss any procedural issues relating to BOOST II, to, monitoring study progress, amend the study protocol if required, and to review the findings of the DSMC

9.3 Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee (DSMC) will be established. It will review interim data and other emerging evidence, including overviews of relevant RCTs. The DSMC will advise the TMC if in their view there is proof beyond reasonable doubt of net clinical benefit or harm, for all infants that might reasonably be expected to influence the management of many clinicians. The DSMC supports the view that a difference of at least 3 standard deviations (SD) in a major endpoint (or in a combination of major endpoints) that suggested net clinical benefit or harm may be needed to justify recommending that the TMC consider either stopping the study prematurely,^{40, 41} monitoring the trial more frequently or modifying the trial design.

9.4 Net Clinical Benefit: an important criterion for decision making

It should be noted that evidence of a significant difference in ROP is not necessarily an indication for early stopping of the trial since this might be balanced by a reduction in deaths or other major disability. For example the higher oxygen saturation level may be associated with an increase in ROP which is statistically significant, but may also be consistent with a reduction in deaths which is not statistically significant, and with net benefit (not statistically significant) for the higher oxygen saturation. Similarly, evidence of a significant increase in an intermediate measure of adverse outcome, such as intraventricular haemorrhage (IVH) or periventricular leukomalacia (PVL) on intracranial ultrasound, in one arm of the study is not necessarily an indication to stop it early, since this might be balanced by an overall reduction in deaths and/ or major disability in the other arm of the study on follow up. Furthermore, major outcomes on follow up will not be determined until two years after trial entry. In both examples, it may be appropriate to continue the trial and indeed other related trials, such as SUPPORT, BOOST II-NZ, BOOST II-UK, COT or US-POST until a clearer picture on net clinical benefit was obtained.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Ethics and Regulatory Compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2001) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004.

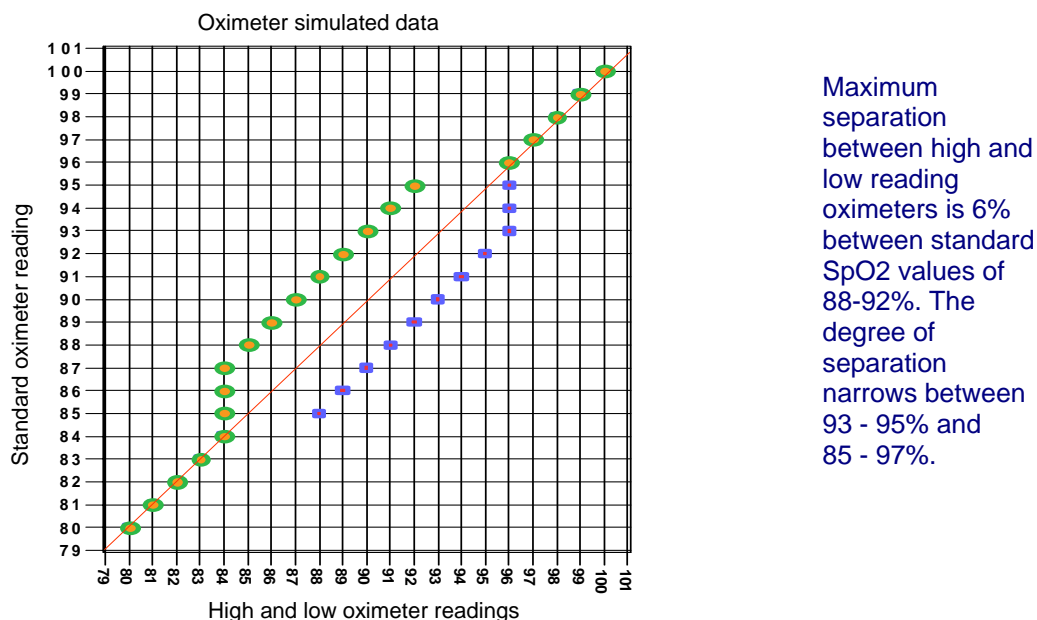
10.2 The importance of adequate compliance with the protocol

Poor compliance while in supplementary oxygen may reduce the difference in SpO₂ between study arms. This would threaten the validity of the trial, by reducing its ability to detect differences in outcome.

The study oximeters provide about 6% separation between high and low reading oximeters compared with a standard oximeter at each of the five SpO₂ values between 88% and 92%, about 5.25% separation at 87% and 93%, about 4.5% separation at 86% and 94% and about 3.75% separation at 85% and 95% (Figure 2). This yields an average difference in SpO₂ between study arms of about 5% (56/11) in the range of displayed values between and including 85%-95% - assuming equal time is spent at each value in that range. The more time spent between 88-92%, the closer to 6% the average difference will be.

Figure 2:

Approximate configuration of study oximeters within the range of values of SpO₂ of 79 – 100%



The more time spent outside the range of 85-95% while in supplementary oxygen, the less the average difference between study arms and the greater the risk that the trial will be inconclusive. Table 1 shows how larger or smaller average differences influence the power of the study.

Table 1 Hypothetical illustration of the effect of varying degrees of separation in average SpO2 between study arms on the power and sample size of the study

Average difference in SpO2 while breathing supplementary oxygen	Difference in death/disability	Power with Sample size of 1200	Sample size to maintain 80% power
6%	9.6%	93%	820
5%	8% (40% vs 32%)	81%	1180
4%	6.4%	61%	1850
3%	4.8%	38%	3280

This assumes for every 1% difference in SpO2 achieved there will a 1.6% difference in death or disability.

The sample of 1200 yields 81% power to detect an average difference of 8% in death or major disability between the two study arms. It is assumed that this difference depends on achieving an average separation of 5% in SpO2 between the two study arms while in supplementary oxygen. If a larger average difference in SpO2 of 6% were achieved (as would occur with a fixed offset of ± 3% across all values) the power of the study would increase to 93% and the sample size needed for 80% power would be only 820. However, if an average difference in SpO2 of only 4% were achieved, the power of the study would fall to 61% and the sample size to maintain 80% power would increase to 1850.

10.3 Compliance with intended target ranges in infants at 27⁶ weeks gestation or less

A pilot study of oxygen targeting during normal clinical practice has shown poor compliance with intended ranges of SpO2 (Appendix A)⁵⁴. The time spent within the intended range while breathing supplementary oxygen varied between 16 - 71%. Most non-compliance was above the intended range. This suggests that specific staff educational programmes may be needed to achieve and sustain adequate compliance. Also, if BOOST II shows that one target produces net clinical benefit, sustained changes in behaviour will be needed to translate this into clinical practice. Two studies report the compliance of caregivers who were motivated by specific education programmes in achieving set targets for infants on respiratory support^{55, 56} (see also Appendix B).

Table 2 Performance in achieving set targets during specific education programmes

	% SpO2 values	% time spent in these ranges while on supplementary oxygen [OWL Project: Goldsmith et al ⁵⁵]	% SpO2 values	% time spent in these ranges while on respiratory support [Rasmussen et al ⁵⁶]
Hyperoxic	96 - 100	9	96 - 100	9
Upper end of widely practised range	93 - 95	22	93 - 96	40
Mid zone	85 - 92	48	88 - 92	29
Lower end of widely practised range			84 - 87	10
Lower than widely practised range	<84	21	< 84	10

In one of these studies,⁵⁵ a new protocol for minimizing exposure to hyperoxia, similar to that employed by Chow et al,³⁶ was adopted by the whole unit. All members of staff signed a contract indicating that they had read and accepted the protocol. The charge nurse made an unannounced visit to every cot in the unit once each shift to document all cases of non-compliance and the reasons. In the other study,⁵⁶

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staff took part in the pilot study of the NICHD multi-centre oxygen targeting trial, SUPPORT, with close supervision from clinicians, respiratory therapists and senior nursing staff. Despite this, caregivers maintained displayed SpO₂ within the central target range of 88 - 92% for only 29% of the time while infants were on respiratory support. Caregivers maintained such infants between 85 - 95% for 70% of the time in the first study⁵⁵ and between 84 - 96% for 79% of the time in the second study.⁵⁶

If inadequate compliance were achieved in the BOOST II trial, this would have substantial impact on study power and sample size, based on the assumptions shown in *Table 1*. Spending an average of 70% of the time within the range 85-95% while on supplementary oxygen might only achieve an average separation between study arms of $0.7 \times 5\% = 3.5\%$. If so, the power to demonstrate a difference in death or disability at two years with a sample size of 1200 would fall from 81% to between 38 and 61%. The sample size needed to preserve 80% power would increase to 3280 (*Table 1*).

One potential barrier to compliance would be the imposition of an arbitrary lower limit of arterial oxygen tension, such as 50 mm Hg (Appendix C), as in the normal range of 50 – 80 mm Hg recommended by the American Academy of Pediatrics,¹⁷ on the basis of consensus rather than fact. It may be helpful for staff to remember that recent studies have suggested that lower oxygen targets may have certain benefits^{16, 25, 26, 33 - 36} and that the normal reference range (95% confidence interval) for fetal PaO₂ is about 22 – 63 mm Hg at 23 weeks gestation, and about 18 – 58 mm Hg at 32 weeks gestation.³⁰ This is equivalent to a range of haemoglobin oxygen saturation of about 60 – 90%.

10.4 Need to determine compliance early on and regularly in BOOST II

All this means that it will be important to develop and evaluate an education programme for accurate oxygen targeting in a small number of NICUs participating in a pilot phase of the BOOST II trial before rolling out the trial to other Australian NICUs. Before participation, each NICU should agree to a careful oxygen monitoring policy, with frequent monitoring and feedback, supported by an education programme for all staff. **If the protocol is closely followed, in some units simply participating in BOOST II may reduce a baby's risk of ROP or chronic lung disease, regardless of which target is assigned. We recommend that each NICU consider adopting a uniform oxygen targeting policy for all infants born at 27⁶ weeks gestation or less, including those who are not recruited to the study.**

Compliance will be measured as the percentages of time spent within the target oxygen saturation range of 88 - 92% and within the range 85 - 95% while infants are in supplementary oxygen. This will be extrapolated to calculate the average difference achieved between study arms. This will be monitored by the TMC, which will remain blinded to all clinical outcomes for the two randomised groups. Only overall rates on clinical outcomes (for the two groups combined) will be provided to the TMC. In the event that an unacceptably small difference in oxygen levels is achieved, the TMC will consider strategies to preserve study power including-

- i) further improving compliance with the target range at each site;
- ii) review of oximeter calibrations;
- iii) extending the range of offset downwards, i.e. from 85-95% to 80-95%;
- iv) a greater sample size, for example by synthesising data from a prospective meta analysis of similar trials. A key point to review this will be at the end of the pilot phase when oxygen saturation levels for between 100 and 200 babies are available.

With 100 babies, with a standard deviation (SD) of 3%, this would give a 90% (confidence interval) CI of $\pm 1.0\%$ on the average difference in oxygen levels and with 200 babies the difference could be estimated with a 90% CI of $\pm 0.7\%$. While major differences from the desired oxygen levels could be seen early, it will be important to continue to monitor the average difference throughout the trial. In addition, the TMC will review the overall event rate in death and major disabilities at time of hospital discharge and at 12 months to project likely 2-year rates.

10.5 Study conduct at each site

All study sites taking part in the trial will be required to participate in a start-up meeting on-site, to present the protocol and undergo training on study procedures and data collection methods. The Principal

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Investigator at each study site must apply for Human Research Ethics Committee (HREC) approval, submit all amendments and changes to the protocol and provide any necessary documentation for their site before they can enroll babies into the study.

The NHMRC Clinical Trials Centre will continually monitor the compliance of study sites taking part. Where non-compliance with the protocol or the standard procedures set out in the Investigator Agreement is suspected, one of the Lead Investigators for the study will contact the study site to resolve any problems. If appropriate, the matter will be referred to the BOOST II Trial Management Committee at their next meeting or by correspondence with members if urgent. The BOOST II Trial Management Committee has the full authority to take appropriate corrective action, including temporary or permanent withdrawal of the study site from BOOST II.

10.6 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC Clinical Trials Centre, University of Sydney and will only be available to staff directly involved in the study.

10.7 Data Handling and Record Keeping

Trial data will be recorded on the e-CRFs provided. All required data entry fields will be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a baby's study-related data.

The following information should be available from into the baby's medical record so that it can later be entered onto the CRF:

- a. Baby's medical record number, baby's initials and study number.
- b. The date that informed consent was obtained.
- c. The date and time the study oximeter was attached to the baby.
- d. Any unexpected serious adverse events.
- e. The date the study oximeter was removed, because the baby was in air, or for any other reason.

All study-related documentation will be maintained for 23 years following completion of the study.

10.8 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (CTC). Monitoring will include centralized review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites for source data verification, review of the investigator's site file and study oximeter handling records. The CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorized CTC staff direct access to their medical records and the study data.

10.9 Audit and Inspection

This study may be subject to audit or inspection by representatives of the CTC or representatives of regulatory bodies (e.g. Therapeutic Goods Administration).

10.10 Clinical Study Report

The data will be entered and analysed by the CTC. Statistical analysis will be conducted by the CTC. A Clinical Study Report will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the international collaborative group undertaking the prospective meta-analysis of neonatal oxygen trials, after it has been approved by the Trial Management Committee.

10.11 Publication Policy

The TMC will appoint a Writing Committee to draft manuscripts based on the trial data. Manuscripts will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication.

10.12 Ancillary Studies

Ancillary studies are encouraged. For example, BOOST II, in collaboration with other neonatal oxygen trials, offers a unique opportunity for a prospective observational meta-analysis of variability in SpO₂ and heart rate in relation to severe retinopathy and neuro-developmental outcome, using continuously recorded oximeter data in a large cohort of very preterm infants. Proposals for ancillary studies should be submitted for approval to the Trial Management Committee.

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ABBREVIATIONS

BOOST	Benefits of Oxygen Saturation Targeting
BPD	Broncho-Pulmonary Dysplasia
CI	Confidence Interval
CLD	Chronic Lung Disease
COT	Canadian Oxygen Trial
CPAP	Continuous Positive Airway Pressure
CRF	Case Record Form
DRG	Diagnostic Related Group
DSMC	Data and Safety Monitoring Committee
e-CRF	Electronic Case Record Form
EPN	Extremely Premature Newborns
ELBW	Extremely Low Birth Weight
FiO ₂	Inspired Oxygen
HREC	Human Research Ethics Committee
ICER	Incremental Cost Effectiveness Ratio
ICH GCP	International Conference on Harmonisation Good Clinical Practice guidelines
ISRCTN	International Standard Randomised Controlled Trial Number
IVH	Intra-Ventricular Haemorrhage
NHMRC	National Health and Medical Research
NICHD	National Institute of Child Health and Human Development
MDI	Mental Development Index
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Units
OWL	Oxygen With Love
Ox	Oximeter
PDA	Patent Ductus Arteriosus
PDI	Psychomotor Development Index
PMA	Prospective Meta-Analysis
POST ROP	Pulse Oximetry Saturation Trials to prevent Retinopathy of Prematurity
PVL	Peri-Ventricular Leukomalacia
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
ROP	Retinopathy of Prematurity
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SD	Standard Deviation
SET	Signal Extraction Technology
SOP	Standard Operating Procedure
SpO ₂	Oxygen Saturation
STOP ROP	Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
SUPPORT	Surfactant Positive Airway Pressure and Pulse Oximetry Trial
TGA	Therapeutics Goods Administration
VEGF	Vascular Endothelial Growth Factor
VON	Vermont Oxford Improvement Network

APPENDIX A

Actual Versus Intended Pulse Oxygen Saturation (SpO₂) in Infants <28 Weeks Gestation⁵⁴

James Hagadorn, Anne Furey, T. Hang Nghiem, Skyler Greene, Ekua Abban, Jennifer Cho, Prashant Shrestha, Ami Vora, Christopher Schmid, Patricia Hibberd, Cynthia H. Cole, The AVIOx Study Group. Division of Newborn Medicine and Division of Clinical Care Research, Tufts-New England Med Ctr, Boston, MA.

BACKGROUND: Detailed data are not available regarding the actual versus intended SpO₂ in infants born <28 weeks gestation (extremely premature newborns, EPNs) in the neonatal period during routine care.

OBJECTIVES: To document actual SpO₂ in EPNs in the first 4 weeks of life during routine care and compare to the level recommended by local policy/guideline.

DESIGN/METHODS: EPNs <96 hours old were enrolled in a prospective multicenter cohort study. Oximetry data were collected every 2 seconds with masked signal-extraction oximeters for 72 hours in each of the first four weeks of life. Data for infants on supplemental O₂ were compared to SpO₂ range prescribed by local institutional policy.

RESULTS: 14 centers from 3 countries enrolled 78 infants with mean birth weight 863 + 208 g and mean gestational age 26 wk + 1.4 wk. Lower limits of intended SpO₂ ranges at study centers varied between 83-92%, upper limits 92-98%. Infants were monitored for median 70 hours in each week. Overall median SpO₂ for infants on supplemental O₂ during the first 4 weeks was 95% (range of study center medians 91-96%). Of 12 centers with defined policies, 11 maintained median SpO₂ within intended range. Proportion of SpO₂ values within intended range varied between 16-71% at different study centers. Most noncompliance was above intended range.

CONCLUSIONS: Median SpO₂ was compliant with intended range at most study centers in this cohort. However, proportion of SpO₂ values in intended range during routine care of EPNs on supplemental O₂ varied substantially among study centers. These data will assist quality improvement and education efforts, and will aid planning of randomized trials examining level of oxygenation.

DISCLOSURE: Funded by the SPR Student Research Program; Fight for Sight/Prevent Blindness America; The Tufts-NEMC Research Fund; GCRC/Natl Center for Research Resources MO1-RR00054, and NEI K23 EY/HD00420. Oximeters provided by Masimo Corp.

APPENDIX B

Prospective Evaluation of Altered Pulse Oximeters Designed To Produce Different Oxygen Exposures for ELBW Infants: Pilot for the SUPPORT Trial⁵⁶

Maynard R. Rasmussen, Wade Rich, Gregory S. Rasmussen, Neil Finer, NICHD Neonatal Research Network. Neonatology, Sharp Mary Birch Hospital for Women, San Diego, CA; Neonatology, University of California, San Diego, San Diego, CA.

BACKGROUND: No prospective studies have evaluated the effect of higher vs. lower SpO₂ ranges in ELBW infants from birth. The SUPPORT trial will randomize ELBW infants to different SpO₂ ranges within 2 hours of birth, using altered Masimo oximeters (Masimo Corp, Irvine, Ca), programmed to display falsely high or low SpO₂ values with a maximum difference of 6% @ 90% (displays 87% or 93%) which tapers to normal at 84% and 96%. The displayed range of 88-92% corresponds to actual values of either 85%-89% or 91%-95%.

OBJECTIVE: To test the performance of altered oximeters (Ox) on ELBW infants prior to the SUPPORT trial to ensure that an adequate separation of SpO₂ is achieved.

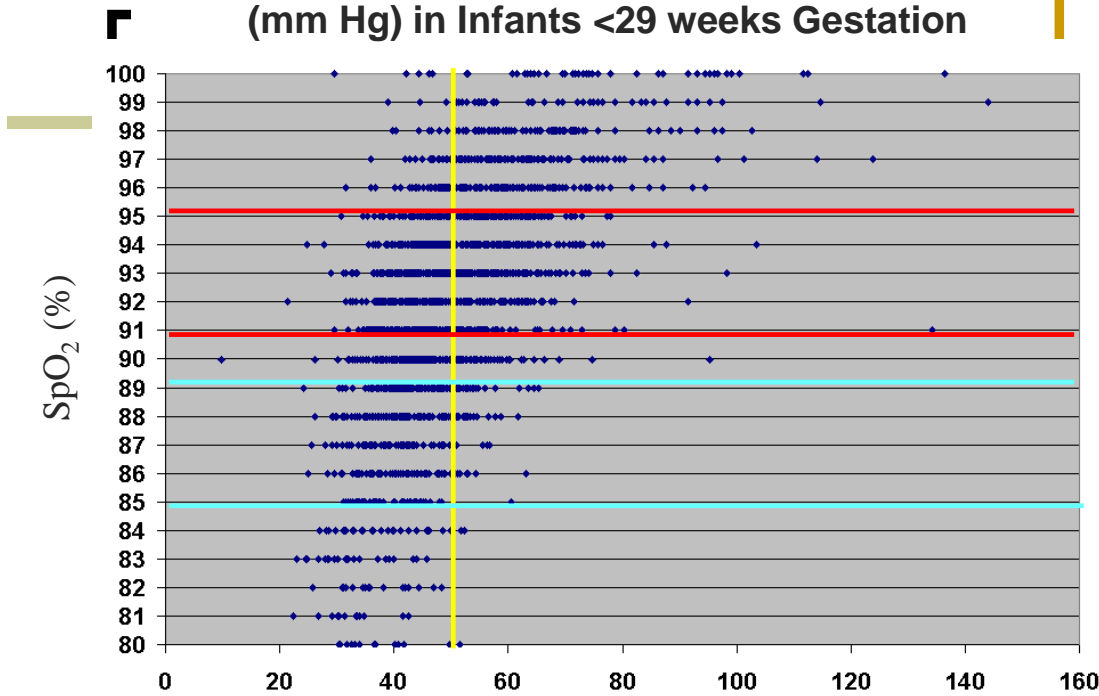
DESIGN/METHODS: Oximeter performance was evaluated on 20 hemodynamically stable ELBW infants receiving positive pressure support, using standard Masimo Oxs. Sensors from a standard and a masked (high or low reading) Ox were attached one to each lower extremity. Ox alarms were 84% and 96% with target SpO₂ of 88% to 92%. Sensors were switched every 6 hours and altered oximeters switched after 12 hours. The averaging mode was 16 seconds, data sampling every 10 seconds and data was collected for 24 hours. Data points were matched to the nearest second.

RESULTS: 1. Contemporaneous Ox data demonstrated a 4.4% difference in mean SpO₂s of altered Oxs at a standard SpO₂ of 90%. The difference between the altered Oxs decreased to <2% for standard SpO₂ values of less than 84% and greater than 96%. 2. Motivated caretakers were successful at maintaining a target SpO₂ of 88-92% for only 29% of the time. Patients spent 10% of time < 84%, 10% between 84% and 87%, 40% between 93% and 96% and 9% of time >96%. 3. The altered oximeters would have resulted in minimal differences in SpO₂ and oxygen exposure.

CONCLUSIONS: Altered Oxs performed as designed, but achieved less clinical separation than anticipated, probably due to saturation averaging and decreasing differences in altered Oxs as 84% and 96% are approached. The narrow target range was maintained for < 1/3rd of time. To achieve a greater difference between groups, we believe that a maximal separation of 6% over a wider range of SpO₂s is desirable, and this algorithm is being developed.

APPENDIX C

Functional Saturation (SpO₂) vs PaO₂ (mm Hg) in Infants <29 weeks Gestation



Unpublished data supplied by courtesy of B Stenson, Simpson Memorial Maternity Pavilion, Edinburgh.

These simultaneous measurements of SpO₂ and oxygen tension were obtained in stable infants with normal blood pressure and blood lactate less than 3 mmol/ L. They illustrate the broad scatter of values of oxygen tension at any given value of SpO₂. It is therefore unlikely that the BOOST II trial would become unmasked by knowledge of simultaneous values of oxygen tension.

However, imposing an arbitrary lower limit of oxygen tension of 50 mm Hg would, in a substantial proportion of cases, make it impossible to achieve actual SpO₂ targets of 85 – 89% or 91 – 95%. It may be helpful to remember that the normal fetal reference range (95% CI) for umbilical venous oxygen tension has a lower limit of about 22 -33 mm Hg at 23 weeks gestation, and a lower limit of about 18 - 23 mm Hg at 32 weeks gestation.^{30, 31}

APPENDIX D
Parent Information and Consent Form



INFORMATION FOR PARENTS

Which oxygen level should we use for very premature infants?

We invite you to join an international study of the **Benefits of Oxygen Saturation Targeting (BOOST II)**

What is the purpose of the study?

- Doctors and nurses worldwide try to give premature babies enough oxygen to keep blood oxygen saturation between 85% and 95%.
- We now need to find out if the upper or lower part of this range is better.
- Too much or too little oxygen for long periods may harm babies' eyes, lungs and brain, in or out of the study.

What does this study involve?

- Premature babies have oxygen levels (saturation) monitored all the time with a pulse oximeter. This doesn't hurt.



These pictures show an oxygen sensor on a baby's foot covered to keep the light out. The sensor is connected to a pulse oximeter (not shown). The oximeter is about as big as a DVD player. This oximeter display shows oxygen saturation at 91% and pulse rate at 144.

- The study will aim to enroll about 1200 babies in Australia and 5,000 worldwide.
- Babies in the study get an oximeter that reads slightly higher (by 3%) or slightly lower (by 3%) than the actual oxygen saturation. The study oximeter is chosen randomly by a computer (like tossing a coin).
- In babies breathing air, the oximeter may read up to 100%. That is normal.
- In babies on oxygen, we aim to keep saturation as close to 88% - 92% as possible with both types of oximeter.
 - the higher study oximeters read 88% - 92% when actual saturation is 3% lower at 85% - 89%
 - the lower study oximeters read 88% - 92% when actual saturation is 3% higher at 91% - 95%
- Above or below the range of 85 – 95% each oximeter will show the true oxygen saturation.
- The staff do not know which oximeters read higher and which read lower. This is the best way to do the study.

Which oxygen saturation level should we use for very premature infants? A randomised controlled trial

- Your baby keeps the study oximeter until oxygen is not needed or until 36 weeks. If your baby needs oxygen treatment after that, your baby will have a standard nursery oximeter.
- We will record any illnesses in hospital and collect data from the study oximeter.
- If your baby goes to another hospital on oxygen before 36 weeks, the study oximeter will go as well. You do not have to sign another consent form.
- We'll phone you at home at 6, 12 and 18 months to ask how your baby is doing. In the follow up clinic at two years from "term", we will check how your baby sees, hears, talks, walks and thinks. This takes about 2 hours and we will pay your travel expenses if necessary.

What are the possible benefits and risks of taking part in this research?

- Babies in the study will benefit by having oxygen monitored even more closely than normal.
- The main benefit is to test which oxygen level is better for babies in future. This may not directly help your baby.
- Too much oxygen for long periods may harm the eyes, brain cells or lung.
- Too little oxygen for long periods may harm brain cells and contribute to chronic lung disease.
- These risks exist whether your baby is in or out of the study.

Confidentiality

Study information that can identify your child will be confidential. Only staff working in the study and other authorised persons can see your baby's study information or medical records. Study information will be stored at the hospital and the Co-ordinating Centre at The University of Sydney for at least 23 years by law.

Participation is Voluntary

You can decide whether or not to allow your baby to take part in this study. You can withdraw consent at any time without giving a reason. If so, we would ask if we can see your child at two years and keep track of your child through the Meidcare Australia database. You do not have to agree.

If you chose not to take part, it would not affect your baby's treatment or your relationship with the staff. Your baby would have oxygen treatment by the nursery's guidelines.

Contacts or Complaints

You can contact either Dr or Dr..... if you have any questions or concerns arising from taking part in this research. Phone during working hours or (page Dr) after hours or by email The Hospital also has a Consumer Advocate available on

In the unlikely event that a child suffers injury as a result of taking part in this study, treatment will be provided by the public health service at no extra cost to you.

Thank you for reading this leaflet. It is for you to keep.

If you join the study, you will also keep a copy of the consent form.

Hospital Letterhead

PARENT CONSENT FORM

Which oxygen level should we use for very premature infants? The Benefits of Oxygen Saturation Targeting study (BOOST II)

I,
Name of Parent/Guardian (please print)

of.....
Address Parent/Guardian (please print)

have read and understood the information for parents on the above named research study and have discussed it with I am aware of the procedures involved in the study, including any inconvenience, risk, discomfort or side effect, and of their implications.

I freely choose to take part in this study and understand that I can withdraw without compromise at any time.

I also understand that the research study is strictly confidential.

I hereby agree for my child to take part in this research study.
Baby's Name (please print)

Signature of parent/guardian:..... Date:___/___/___

Name of witness/ interpreter:..... Signature:.....

Date:___/___/___

Name of person obtaining consent:.....

Signature of person obtaining consent:..... Date:___/___/___

I authorise Medicare Australia to provide updated details of my residential address, as held on Medicare records, to the BOOST II Coordinator, NHMRC Clinical Trials Centre, Locked Bag 77, Camperdown, 2050. This consent remains valid for 5 years from the date this consent is signed.

Medicare number of parent/guardian: _____

Name of parent/guardian:..... Signature:..... Date:___/___/___

Name of witness/ interpreter:..... Signature:.....

Date:___/___/___

Hospital Letterhead

TELEPHONE CONSENT TO PARTICIPATE IN BOOST II

For use if parents of an eligible baby cannot reach the Neonatal Intensive Care Unit within an appropriate time, in the opinion of the most senior clinician available.

Which oxygen level should we use for very premature infants? The Benefits of Oxygen Saturation Targeting study (BOOST II)

Name of Investigator: _____

The parent named below has read the *BOOST II Information for Parents* leaflet, or has been given the information orally, and has agreed that their baby can participate in BOOST II yes no

The parent understands that he or she is free to leave the study:

- at any time yes no
- without having to give a reason for leaving yes no
- and without affecting their baby's medical care yes no

The parent has been read the information in the consent form, and understands that he or she will be asked to sign the separate consent form on their next visit to the hospital. yes no

Name of parent/guardian spoken to:

Name of parent who gave consent for participation in BOOST II (if different from above):

Name of health professional who obtained consent:

Name of witness:

Signature of witness:

Relationship to participant of independent witness: _____

**Independent witness is not the investigator nor his/her delegate.*

Date and time of telephone call: ___/___/_____
dd/mm/yyyy

24 hour

****The parent's consent form must be signed on the next visit to hospital****

Enter the date when the parent's consent form is signed: ___/___/_____
dd/mm/yyyy