_____

A RANDOMISED CONTROLLED TRIAL OF OXYGEN THERAPY ON GROWTH AND DEVELOPMENT OF PRETERM INFANTS

Lisa Askie

April 2003

School of Public Health

Centre for Perinatal Health Services Research

University of Sydney

This thesis is submitted in total fulfilment of the requirements for the

degree of Doctor of Philosophy, University of Sydney

_____

ABSTRACT

Background

Physiological studies have shown that many preterm infants and infants with chronic lung disease may suffer chronic hypoxaemia, which possibly leads to poor growth and development. Anecdotal reports indicate that there is a drive to increase the oxygen saturation target range to a higher level in these infants due primarily to perceived benefits derived from clinical experience and from uncontrolled observational studies of babies discharged on home oxygen.

Objective

The BOOST (Benefits Of Oxygen Saturation Targeting) trial is the first randomised trial to assess the long-term benefits and harms of two different oxygen saturation target ranges.

Methods

BOOST was a multicentre, double blinded, randomised controlled trial that enrolled 358 infants born at less than 30 weeks' gestation who remained oxygen-dependent at 32 weeks postmenstrual age. They were randomly assigned to target either a functional oxygen saturation range of 91-94% (standard or control group) or 95-98% (higher or treatment group). The primary outcomes were growth and neurodevelopmental measures at 12 months corrected age. Secondary outcomes included length of hospital stay, retinopathy of prematurity, health service utilisation, parental stress, and infant temperament.

Results

Prognostic baseline characteristics did not differ between the two groups. Mean birth weight and gestational age of enrolled infants was 917g and 26.5 weeks respectively. The rate of antenatal corticosteroid use was 83%.

_____

There were no significant differences in any of the short-term growth outcomes (weight, length, head circumference at 38 weeks postmenstrual age). Of the 334 infants with complete primary outcome data (93% of infants enrolled, 97% of survivors to 12 months corrected age), 39/168 infants (23.2%) in the treatment group had a major developmental abnormality, compared with 40/166 infants (24.1%) assigned to the control group (RR 0.96, 95% CI 0.66 to 1.42, P=0.8). Similarly, 55/168 infants (32.7%) with complete growth data in the high saturation target range group had a weight less than the 10th centile at 12 months corrected age, compared with 61/165 infants (37.0%) in the control arm (RR 0.89, 95% CI 0.66 to 1.19, P=0.4). No significant differences were found in mean weight, length or head circumference at 12 months corrected age between the two groups. When the primary outcomes were examined in the pre-specified sub-group of infants less than 28 weeks' gestation at birth, and in the sub-group of infants who went home on supplemental oxygen, all results remained non-significant.

There were 9 post-randomisation deaths in the higher oxygen group and 5 in the standard group (RR 1.78, 95% CI 0.61 to 5.21, P=0.3). Of the secondary outcomes examined, the higher saturation target group had a statistically significantly longer duration of oxygen (P<0.0001), and increased rates of oxygen dependency at 36 weeks postmenstrual age (RR 1.40; 95% CI 1.15, 1.70; P=0.0006) and home oxygen (RR 1.78; 95% CI 1.20, 2.64; P=0.004). There were no statistically significant differences in any of the other pre-specified secondary outcomes including days of ventilation, length of hospital stay, time to full sucking feeds, worst stage of retinopathy of prematurity, health service utilisation, or measures of postnatal depression, infant or toddler temperament, parenting stress, or family impact.

Conclusions

Targeting a higher oxygen saturation range in chronically oxygen-dependent, extremely preterm infants conferred no significant long-term growth or development benefits but did increase their duration of oxygen, rate of home oxygen and need for supplemental oxygen at 36 weeks postmenstrual age.

ACKNOWLEDGMENTS

_____

This thesis is dedicated to Les Chermignonards D'esenchant'es who, having called for collaborative trials to resolve the issue of oxygenation in preterm infants 25 years ago, have finally seen some results. Salut!

Les Chermignonards D'esenchant'es. Oxygen and retrolental fibroplasia. *Pediatrics* 1977; 60: 753-754.

AUTHOR'S CONTRIBUTION

The author of this thesis undertook the following aspects of the project:

- **protocol development**: including formalising the final stages of the protocol development, suggesting and making minor modifications after commencement, and creation of all data collection forms.

- **funding application submissions**: writing all but the initial funding submissions, institutional ethics committee applications and ongoing progress reports.

- **literature review**: responsible for undertaking an extensive pre-trial literature review and four Cochrane systematic reviews related to the topic as well as regularly updating these reviews.

- **project management**: management of all personnel, budget and finance, infrastructure, merchandise, inservice education, on-call service, transport, equipment maintenance, and correspondence related to the project.

- **data collection and database management**: establishment of variables to be collected, overseeing the database creation by an external consultant, supervision of data collection by the research nurses and clinical staff, data entry, data checking and quality control procedures, management of data files, ensuring data security and confidentiality.

- **data analysis**: responsible for planning and undertaking all data analyses including writing all data analysis programs and executing all the analyses.

- **interpretation of results**: responsible for, and author of, all aspects of the interpretation of results as outlined within the thesis.

- **writing manuscripts for publication of findings**: responsible for the production of all major papers relating to the project, mostly as first author.

- **presentation of findings**: author of over 15 national and international presentations, oral papers and posters, summarising and presenting the project's findings.

_____

The PhD supervisors, Professors David Henderson-Smart, Les Irwig and Judy Simpson were involved in the formulation of the research question and initial protocol development. They gave ongoing advice regarding project management, data collection issues, data analysis, results interpretation and the presentation of the study's findings but did not have primary responsibility for these aspects of the project.

Ms Sharon Kidd also made significant contributions to the formulation of the research question, and the original protocol development, ethics committee and funding application submissions.

_____

DECLARATION OF AUTHENTICITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and is less than 80,000 words in length. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference has been made.

Lisa Maree Askie

TABLE OF CONTENTS

ABBREVIATIONS

ACT - Australian Capital Territory

BOOST - Benefits of Oxygen Saturation Targeting Trial

BPD - bronchopulmonary dysplasia

CI - confidence interval

CLD - chronic lung disease

cm - centimetres

corr - corrected age (chronological age plus weeks of prematurity)

CP - cerebral palsy

CPAP - continuous positive airway pressure

dev abn - developmental abnormality

DHS - David Henderson-Smart (chief investigator)

DQ - development quotient

DRG - diagnosis related group

ECC - Early Childhood Centre

ECMO - extracorporeal membrane oxygenation

ELBW - extremely low birthweight (birthweight less than 1000 grams)

EPDS - Edinburgh Postnatal Depression Scale

ETT - endotracheal tube

extremely preterm - infant born before 28 completed weeks' gestation

FiO_2 - fraction of inspired oxygen (a measure of oxygen concentration)

g - grams

GA - gestational age (completed weeks since first day of last menses)

GP - general practitioner

h - hour

hc - head circumference

HFV - high frequency ventilation

ICU - intensive care unit

IFS - Impact on Family Scale

_____

IQR - interquartile range

ITS - Infant Temperament Scale

IVH - intraventricular haemorrhage

JMS - Judy Simpson (chief investigator and trial statistician)

kg - kilograms

LBW - low birthweight (birthweight less than 2500 grams)

LI - Les Irwig (chief investigator)

LMA - Lisa Maree Askie (trial coordinator)

l/min - litres per minute

LOS - length of (hospital) stay

MD - mean difference

MedD - median difference

ml/dl - millilitres per decilitre

mmHg - millimetres of mercury (a unit of measurement)

mth - month

N - number

NEC - necrotising enterocolitis

NH&MRC - National Health and Medical Research Council

NICU - neonatal intensive care unit

NNH - number needed to harm

NNT - number needed to treat

NSW - New South Wales

O_2 - oxygen

PaO_2 - partial pressure of arterial oxygen (a measure of blood oxygen level)

PAP - pulmonary artery pressure

$PcapO_2$ - partial pressure of capillary oxygen (a measure of blood oxygen level)

PDA - patent ductus arteriosus

pma - postmenstrual age (time in weeks or months since last menses: gestational age plus postnatal age)

postnatal age - age in weeks or months since birth

PSI - Parenting Stress Index

preterm - born before 37 completed weeks of gestation

PVL - periventricular leukomalacia

PVR - pulmonary vascular resistance

Rev Griffiths - Revised Griffiths Mental Development Scale

RCT - randomised controlled trial

RR - relative risk

RLF - retrolental fibroplasia

ROP - retinopathy of prematurity

SD - standard deviation

SaO_2 - oxygen saturation level of arterial oxygen (a measure of blood oxygen level)

SIDS - Sudden Infant Death Syndrome

SMC - safety monitoring committee

SpO_2 - oxygen saturation level using pulse oximetry (a measure of blood oxygen level)

$TcPO_2$ - trancutaneous partial pressure of oxygen (a measure of blood oxygen level)

TPN - total parenteral nutrition

TTS - Toddler Temperament Scale

VGEF - vascular endothelial growth factor

VLBW - very low birth weight (birthweight less than 1500 grams)

wks - weeks

wt - weight

UK - United Kingdom

- number

1.1 <u>Introduction</u>

Babies with lower gestational ages are increasingly represented in neonatal intensive care units (NICUs) today, due to enhanced survival prospects.[1, 2] However, the increased survival of these infants has been associated with increased measures of chronic ill health including chronic lung disease of infancy.[3] This condition, currently defined as continued oxygen dependency at 36 weeks postmenstrual age (pma),[4, 5] has become a major clinical challenge as chronic lung disease is accompanied by significant morbidity including poor growth,[6-17] neurological impairment[14, 16] and adverse pulmonary sequelae.[14, 18] These infants are on extended stays on supplemental oxygen until they can maintain normal breathing patterns which results in considerable health service costs.[19-23]

1.2 <u>Oxygen therapy</u>

Supplemental oxygen is probably *the* most common treatment given to infants in the newborn period.[24] Increasing the oxygen concentration of inspired air (FiO_2) is the oldest and most widely used method of correcting the hypoxia that frequently affects newborns adapting to the ex-utero environment.[25] Despite its documented use in infants for over 75 years,[26] there are very few randomised controlled trials which have studied the most appropriate ranges to maintain oxygen levels for either term or preterm infants, or a threshold value below which oxygen should be administered.[25, 27]

Each year over 5,000 infants (or approximately 2% of all infants born) in Australasia receive oxygen therapy during their initial stay in a neonatal intensive care nursery and more than 300 of these infants require continued oxygen therapy at home after discharge.[28] The incidence of oxygen therapy is dependent on gestational age at birth with 96% of infants born at less than 28 weeks' gestation receiving supplemental oxygen, whilst only 75% of infants born between 28 and 31 weeks require oxygen therapy during their initial hospitalisation.[28] Similarly the incidence of chronic lung disease (defined as supplemental oxygen and/or assisted ventilation

at 36 weeks postmenstrual age) decreases from 45% in infants born at less than 28 weeks to 12% for those born between 28 and 31 weeks' gestation. [28]

1.3 Normal oxygen values

In the past, establishing appropriate parameters for oxygen therapy had been difficult because of the lack of information at the time regarding the safe use of oxygen.[24] A balance has now been achieved between preventing adverse effects to the eye, in particular, retinopathy of prematurity (ROP), and decreasing the mortality of preterm infants.[27]

There have been several attempts to quantify normal or reference values of oxygen saturation (SpO_2) and/or partial pressure of arterial oxygen (PaO_2) levels for both term and preterm infants.[29-35] These data are summarised in Figure 1 below: [27]

Figure 1: Reference data for SpO_2 in infants

		Age (days)		Baseline SpO_2 (%)			
					Minimum		
# Subjects	Type	Median	Range	Median	Value	5th centile	Reference
55	pt a	1	1-7	99.4	90.7	95.7	29
160	pt b	20	3-165	99.6	88.7	95.7	30
110	pt b	62	30-176	100.0	95.3	97.9	30
90	ft	<1	5-23 hrs	98.3	88.7	95.2	31
60	ft	4	1-7	97.6	92.0	93.2	32
60	ft	17	8-28	98.0	86.6	91.9	32
66	ft	39	29-54	99.8	97.0	97.5	33
16	ft	102	83-146	99.9	98.6	99.2	34

Baseline SpO_2 measured during regular breathing, at least 10 seconds away from sighs and apnoeic pauses, using a Nellcor N200 pulse oximeter which measures functional saturation. Listed are the median and lowest values found in the study and the fifth centile.
pt, preterm; ft, full-term.
a Median gestational age at birth: 35 weeks (range 30-36).
b Mean gestational age at birth (for both groups): 32.5 weeks (SD 2.5).

These studies demonstrated a relatively narrow range of normal baseline SpO_2 values during regular breathing, that is, in quiet sleep. For preterm and term infants this is 93-100% (0-28 days age) and for term infants 97-100% (2-6 months age).[27] These data correspond with the few existing studies of arterial partial pressures of oxygen which have demonstrated mean PaO_2 of 70-76mmHg in term infants on day 2-7 of life.[35] In contrast, desaturation episodes are common in both term and preterm infants in the early neonatal period, but decrease markedly with age (see Figure 2).[27]

Figure 2: Reference data for SpO$_2$ in infants - desaturations

| | | | Age (days) | | Desaturations | | |
| | | | | | % Recordings | # per 12 h Recording | |
# Subjects	Ref	Type	Median	Range	with Desats.	# Desats.	95th Centile
55	[29]	pt a	1	1-7	18	55	8
160	[30]	pt b	20	3-165	71	355	61
110	[30]	pt b	62	30-176	31	17	3
90	[31]	ft	<1	5-23 hrs	26	34	6
60	[32]	ft	4	1-7	35	41	16
60	[32]	ft	17	8-28	60	165	32
66	[33]	ft	39	29-54	16	9	2
16	[34]	ft	102	83-146	6	1	0

Desaturation was defined as a fall in SpO$_2$ to $\leq$80% for at least 4 seconds with the pulse oximeter (Nellcor N200) in a beat-to-beat mode and analysed in both regular and non-regular breathing.

However, the most appropriate range of oxygen saturation or oxygen tension to target, for both term and preterm infants, either in the early newborn period or later, remains largely unanswered by the current available research evidence. In 1992, the American Academy of Pediatrics recommended an arbitrary PaO$_2$ range of 50-90 mmHg.[36]

1.4 Oxygen monitoring methods

The most appropriate method of monitoring and assessing adequate oxygenation in the neonate remains controversial. There are several different ways of measuring blood oxygen levels in neonates and all methods have advantages and disadvantages.

The partial pressure of oxygen in arterial blood (PaO$_2$) can be measured directly via indwelling intra-arterial catheters which are sampled intermittently or by taking arterial puncture samples when required. Because PaO$_2$ in the newborn is quite labile,[37, 38] intermittent measures may not reflect an infant's steady state oxygen level.[25] These measurement methods also have a high risk of complications when used in newborns such as haemorrhage due to dislodgement and the need for top-up blood transfusions if sampling is frequent due to the newborn's low circulating blood volume.

Hence, the development of continuous, non-invasive methods of measuring blood oxygen levels in neonates have been developed in recent years. Transcutaneous measurement of the partial pressure of oxygen (TcPO$_2$) was a technology developed in the 1970s. TcPO$_2$ is

measured with a sensor which incorporates a miniature Clark electrode and which is applied to the skin and heated in order to increase capillary blood flow. The combination of several factors (hyperperfusion, heat-induced shift of the oxyhaemoglobin dissociation curve and increased tissue oxygen consumption) result in the "arterialising" of the blood in the capillary bed below the sensor and the resulting $TcPO_2$ level approximates the actual arterial oxygen level well in most circumstances.[25]

The anticipated benefits of continuous, non-invasive oxygen monitoring methods have not, however, necessarily resulted in significant improvements in the outcomes that they were designed to affect, such as retinopathy of prematurity (ROP).[25, 39] The sensitivity and specificity of detecting hypoxia (PaO_2 <50mmHg) and hyperoxia (PaO_2 >80-100mmHg) using transcutaneous monitors have been estimated at 83% and 98%, and 87% and 90% respectively.[25] The effect of continuous transcutaneous monitoring on the incidence of ROP has had varying results. Some non-randomised studies[40, 41] have claimed a near abolition of ROP using $TcPO_2$ monitoring whilst others[42] have reported no difference in the incidence or severity of ROP attributable to $TcPO_2$ monitoring. The only randomised trial[43-45] to date which has examined the effect of transcutaneous monitoring (continuous $TcPO_2$ monitoring versus standard care) on ROP incidence suggested a modest improvement in ROP rates for infants with greater than 1000g birthweight, but no effect on smaller infants in whom ROP occurs more frequently and is more severe. Conversely there was a trend to higher mortality in the group receiving continuous transcutaneous monitoring, and the rates of the combined outcome, death or ROP, were nearly identical in the two groups. Also, this trial did not detect any effect of transcutaneous monitoring on the incidence of chronic lung disease. It has been hypothesised that it is the variability of oxygen levels rather than a threshold upper level that might be the main contributing factor to the development of ROP in at-risk infants.[46-48]

Oxygen saturation monitoring using pulse oximetry has gained widespread use in neonatal nurseries since the early 1980s due to its ease of use and lack of heat-related side effects, particularly in extremely preterm infants with sensitive skin, despite very little evidence of its effectiveness on clinically important outcomes.[25] Pulse oximetry (SpO_2) refers to the estimation of the oxygen saturation of arterial blood (SaO_2) using a device that measures the

pulsatile changes in light transmission across a tissue bed. Oximeters work on the principle that desaturated haemoglobin and oxygenated haemoglobin absorb light of different wavelengths (red and infrared). The oximeter emits light of these two wavelengths and measures absorption in the pulsatile element of the blood flow, thus producing a measure of the oxygen saturation of arterial blood separate from the non-pulsatile venous blood.[49] Pulse oximeters measure either functional or fractional oxygen saturation. Functional saturation is the ratio of oxyhaemoglobin to the sum of oxyhaemoglobin and deoxyhaemoglobin. Fractional saturation measures the ratio of oxyhaemoglobin to the sum of all four haemoglobin species in the blood, including both functional and dysfunctional haemoglobins (see formulae below).[50, 51]

$$\text{Functional saturation} = \frac{\text{oxyHb}}{\text{oxyHb} + \text{deoxyHb}}$$

$$\text{Fractional saturation} = \frac{\text{oxyHb}}{\text{oxyHb} + \text{deoxyHb} + \text{COHb} + \text{metHb}}$$

oxyHb = oxyhaemoglobin
deoxyHb = deoxyhaemoglobin
COHb = carbonmonoxyhaemoglobin
metHb = methaemoglobin

Readings from these two types of oximeters are not interchangeable with functional saturation readings being approximately 2% higher than those obtained from fractional oximeters.[52, 53]

The evidence from non-randomised studies suggests that pulse oximetry is a reliable measure of oxygenation in infants with chronic lung disease and prolonged oxygen dependency, particularly at lower PaO_2 levels.[54-56] The only randomised trial of pulse oximetry monitoring in infants was performed in patients undergoing surgery.[57] This study suggested the value of pulse oximetry in detecting major hypoxic events in anaesthetised children. However, the ability of pulse oximeters to reliably detect hyperoxia[58-60] remains controversial with most authors suggesting that oxygen levels should be corroborated with intermittent arterial blood gas estimations,[61] and/or pulse oximeters should be used in conjunction with, rather than as a replacement for, transcutaneous monitoring[62, 63] where possible.

1.5 <u>Chronic lung disease of infancy</u>

1.5.1 <u>Description</u>

Chronic lung disease of infancy (CLD) was originally defined as oxygen dependency and abnormal chest X-ray changes at 28 postnatal days[64] and was known as bronchopulmonary dysplasia (BPD). This definition was devised at a time when very few infants less than 32 weeks pma survived and hence these infants would be at a minimum of term equivalent age at one month, or 28 days, of life. More recently chronic lung disease has been defined as continued oxygen dependency at 36 weeks postmenstrual age (pma)[4, 5, 65-68] in line with the increasing survival of extremely preterm infants. In today's NICUs infants born as early as 22-23 weeks pma are surviving and hence it would be unrealistic to expect that such infants would be mature enough at 28 days of life to not need supplemental oxygen, when their postmenstrual age was only 26-27 weeks. In this population of extremely preterm infants the continued need for supplemental oxygen at 36 weeks postmenstrual age is far more predictive of the severity of lung disease.[69] The pathophysiology of the disease in today's more extremely preterm infants differs from the original histopathological changes described by Northway in 1967.[64] This so called "new BPD" results in more distal lung injury, characterised by derangements in elastic fibre architecture, airway muscle thickening, alveolar hypoplasia and saccular wall fibrosis, but with minimal bronchial changes.[70] The histopathology of the "new" CLD / BPD indicates an interference with the normal anatomical development of the lung, which may prevent subsequent lung growth and development.[65]

1.5.2 <u>Risk factors and prevention strategies for chronic lung disease</u>

The major risk factor for needing oxygen therapy is extreme prematurity.[28, 71-73] Additional risk factors for prolonged supplemental oxygen include a long duration of assisted ventilation,[74] lack of antenatal steroids,[75] and other antenatal risk factors such as maternal *Ureaplasma urealyticum* infection.[72] As these factors are strong independent predictors of chronic lung disease, a randomised controlled trial study design is important when investigating the effects of treatments for CLD to ensure baseline comparability of these risk factors.

The prevention of chronic lung disease remains elusive, ultimately depending on avoiding or delaying preterm birth whenever possible.[76] However, several other strategies have been suggested to prevent extremely preterm infants developing chronic oxygen-dependency. These include the prevention of oxygen toxicity and barotrauma by the use of treatments such as endogenous surfactant, high frequency ventilation, nitric oxide and extracorporeal membrane oxygenation (ECMO),[77] and the early use of nasal CPAP, as well as prophylactic treatment of patent ductus arteriosus, nutritional supplementation, postnatal steroids and diuretics, blood transfusions, bronchodilators, methylxanthines, and respiratory syncytial virus prophylaxis.[78] Although many of these treatments have short-term benefits, none has been shown to significantly alter the natural history of the condition.

1.5.3 Summary of existing evidence regarding chronic lung disease

Physiological studies have found that infants with chronic lung disease have increased rates of oxygen consumption[79] and lower baseline oxygen saturation levels leading to more frequent desaturation episodes[80, 81] compared with infants without chronic lung disease. It is hypothesised that these infants may be spending a substantial amount of time under-oxygenated, and that this chronic hypoxaemia may possibly lead to poor growth and development.[82] Observational studies have suggested improved sleep patterns,[82, 83] growth and neurodevelopment[84, 85] amongst preterm infants permitted more liberal oxygen supplementation, either in duration or by aiming for higher blood oxygen levels. However, because of the uncontrolled nature of these studies it is not known whether these associations are causal. Anecdotal reports from neonatologists indicated that there had been a drive to increase the oxygen saturation targets to a higher level than is currently maintained by the policies of most neonatal intensive care units. This was due primarily to perceived benefits, derived from clinical experience and from uncontrolled observational studies of babies discharged on home oxygen.[86]

1.6 Effects of differing target oxygen levels on outcomes

There are wide-ranging consequences of adopting differing policies with regard to which infants require supplemental oxygen, what range to target that oxygen therapy and for how long infants should receive supplemental oxygen. A policy of more liberal oxygen therapy

(that is, aiming for higher infant oxygen levels) compared with one that is more restrictive (and thus targets lower oxygen levels) may affect mortality and morbidity including the incidence of CLD, home oxygen rates, days in hospital, incidence of ROP, feeding and sleeping patterns, respiratory outcomes, use of health care services, and short and long-term growth and development measures.

There are very few controlled studies that have investigated the effects of oxygen therapy interventions that are relevant to current neonatal populations and management. The following review summarises the existing evidence on the effects of differing oxygen therapy policies and/or interventions on a variety of outcomes (both physiological and clinical), for term or preterm infants, with either acute or chronic respiratory disease.

1.6.1 Mortality

1.6.1.1 Early mortality

A Cochrane systematic review[87] (by the author and supervisor of this thesis) showed that one randomised trial[88] of targeting either restricted (supplemental oxygen only if PaO_2 <40mmHg) or liberal oxygen therapy ($FiO_2 \geq 0.40$ for 72 hours to keep PaO_2 40-120mmHg) showed no difference in early mortality (20/74 deaths in the restricted oxygen group vs 23/76 in the liberal oxygen group, RR 0.89, 95% CI 0.54, 1.48). Similarly, the multicentre Cooperative trial[89] which compared restricted (supplemental oxygen only if clinically indicated, maximum FiO_2 0.50) and unrestricted ($FiO_2 \geq 0.50$ for 28 days) oxygen policies in infants born at less than 1500g birthweight, who survived more than 48 hours, showed no significant difference in death rates (36/144 in the restricted group vs 15/68 in the liberal group, RR 1.13, 95% CI 0.67-1.92). However, these trials were undertaken in the era before modern neonatal intensive care and none tested the intervention in the critical first 48 hours of the infant's life when mortality effects could be expected to be the most marked.

1.6.1.2 Late mortality

A randomised trial of restricted ($FiO_2 \leq 0.50$, only administered for cyanosis) compared with unrestricted oxygen exposure (mean FiO_2 0.69, given routinely for 14 days or more or until the infant's weight reached 1500g) in 1000-1850g infants[90] showed no significant difference

in death rates during the first 3 months life (12/41 for restricted oxygen vs 9/45 for liberal oxygen administration, RR 1.46, 95% CI 0.69-3.11). The effects of trials of restricted versus liberal oxygen exposure on mortality in preterm or low birthweight infants are summarised in a Cochrane review[87] and reveal no significant difference in late mortality (45/185 for restricted oxygen vs 24/113 for liberal oxygen administration, RR 1.23, 95% CI 0.80, 1.90). Again however, these trials were undertaken in an earlier era when actual measurement of infant blood oxygen levels was not possible and it is thus difficult to extrapolate these results to infants cared for today. A United Kingdom (UK) population-based cohort study[91] of infants born before 28 weeks during 1990-1994 showed no difference in the proportion who survived infancy between infants given enough supplemental oxygen to maintain SpO_2 88-98% for at least the first 8 weeks of life compared with those only given enough oxygen to maintain an oxygen saturation of 70-90%. It should be noted that this study was not a randomised trial and therefore factors which could have potentially confounded these results, such as inter-unit variation in the type and intensity of oxygen monitoring, cannot be ruled out.

Uncontrolled studies[92, 93] and anecdotal evidence[94] suggest targeting a SpO_2 level of 93% or above reduces post-neonatal mortality in infants with chronic lung disease.

1.6.2 Ophthalmic

Retinopathy of prematurity (ROP) is a common retinal neovascular disorder occurring almost exclusively in infants born at less than 30 weeks gestation.[28] In most of these infants the abnormal retinal vasculature regresses and the ROP resolves. However in a small percentage of infants the abnormal vessels continue to grow leading to hemorrhagic and eventually fibrotic retinal scarring and detachment.[95] Severe ROP may result in unfavourable visual outcomes in 40 - 50 percent of cases at 1 year follow up compared to less than 1 percent of infants with no or less severe ROP.[96] Even with treatment, severe ROP is associated with unfavourable visual outcomes in approximately 11 percent of cases at 3 months of age.[97] Retrolental fibroplasia (stage 3 ROP with plus disease[98]) has been associated with supplemental oxygen administration since the 1950's when it was shown that unrestricted oxygen exposure for premature infants regardless of clinical requirement resulted in a significant increase in this condition[87]

Current treatment for severe retinopathy is invasive and involves ablation of the avascular retina by cryotherapy[99] or laser photocoagulation.[97] Non-invasive treatments of ROP have been postulated. One of these is supplemental oxygen therapy aimed at targeting higher oxygen levels in the blood. The physiology behind the postulation that supplemental oxygen can halt and reverse the progression of ROP is as follows. In the first phase of ROP exposure of the extremely preterm infant to the relatively hyperoxic extra-uterine environment after birth leads to down regulation of vascular endothelial growth factor (VEGF) production and the cessation of normal blood vessel growth.[100] The density of blood vessels in the retina is then insufficient once the metabolic demand from the avascular retina increases. A rebound overproduction of VEGF to compensate for the tissue metabolic imbalance leads to the abnormal vascularization typical of ROP.[101] Kittens with hyperoxia-induced ROP that recovered in 28% oxygen had less severe retinopathy than those recovered in room air.[102] Unfortunately the animal models of ROP do not progress to full detachment and blindness as ROP does in some infants and therefore may not completely reflect the pathophysiology in humans.[102]

Although there is broad agreement that restricted versus liberal oxygen policies significantly reduce the incidence of severe ROP,[87, 95, 103, 104] there is little research into what constitutes a safe upper limit of oxygen in the blood in the early neonatal period to prevent ROP. In addition to the available trials, a cohort study also found a significant association between duration of exposure to high levels of oxygen tension, as measured by transcutaneous monitoring, and the incidence and severity of ROP.[105] A UK cohort study[91] of infants born before 28 weeks during 1990-1994 showed that infants given enough supplemental oxygen to maintain SpO_2 at 88-98% for at least the first 8 weeks of life developed severe ROP four times as often as infants only given enough oxygen to maintain an oxygen saturation in the 70-90% range (27% vs 6%, P<0.01). Of note however, is that the severe ROP rate in the lower oxygen range group in this study (6%) is similar to the current Australasian rate for infants less than 28 weeks' gestation at birth (7%), despite considerable practice variation within this region with respect to oxygen saturation target ranges[86] which would encompass both ranges targeted in the UK cohort study.

The use of supplemental oxygen in the SpO_2 96-99% range has been tested in one large, multicentre randomised trial, the STOP-ROP trial,[106] and was found to have no significant effect on rates of progression of pre-threshold ROP. However, in this trial treatment allocation was not masked to caregivers and it has been criticised for having insufficient sample size to detect the expected differences due to the trial being stopped early because of flagging recruitment. Conversely, the results of several case-control studies,[107-109] animal models,[102, 110] and retrospective audits[111] conducted prior to the STOP-ROP trial are consistent and suggest supplemental oxygen reduces the progression of pre-threshold ROP.

1.6.3 Growth

1.6.3.1 Early growth

The Tin UK cohort study[91] showed infants nursed at higher oxygen saturations (88-98%) were more likely to have a weight below the third centile at discharge (45% vs 17%, P<0.01). There have been no controlled trials that have directly assessed the effects of different target oxygen ranges on either short or long-term infant growth. In the STOP-ROP trial,[106] there was no difference in short-term growth measures between the two groups of preterm infants with pre-threshold ROP randomly allocated to target either SpO_2 89-94% or 96-99%, although this was only assessed as a secondary outcome. A case control study in Western Australia reported that infants with chronic lung disease achieved full sucking feeds status approximately one week later than matched preterm controls.[13]

1.6.3.2 Long-term growth

Although there are no controlled trials that have directly assessed the effects of different target oxygen ranges on long-term infant growth, there is ample observational data to support the hypothesis that inadequate oxygenation contributes to poor long-term growth in preterm/low birthweight (LBW) infants with a diagnosis of CLD or BPD.[9, 12, 15, 112] Compared with non-BPD infants, outcomes for these infants include a greater proportion small for their age, and poor catch-up growth. Growth following home oxygen therapy has only been examined in poorly controlled or uncontrolled circumstances. Some studies of home oxygen sufficient to maintain SpO_2 ≥92-95% have reported improvements in weight gain,[84, 85] whilst others have demonstrated continued poor growth compared with non-BPD infants.[113]

Indirect evidence of poor weight gain following impeded oxygenation comes from prospective cohort studies of infants with congenital heart disease[6] and children with chronic asthma.[114] These studies showed that chronic respiratory insufficiency (defined as PO_2 <70mmHg at assessment or asthma onset before 3 years of age) appear to be related to poor growth, although these effects were confounded by the use of corticosteroids.

1.6.4 Neurodevelopment

The Tin UK cohort study[91] showed no difference in the proportion of infants with cerebral palsy at 2 years of age between infants nursed at lower oxygen saturations (SpO_2 70-90%) and those given enough supplemental oxygen to maintain oxygen saturation between 88-98% during the early weeks of life. However, the rates of cerebral palsy seen in both groups were high at approximately 16% and, despite excellent follow-up rates, it should be noted that as this study was not a randomised trial, causality cannot be inferred from this association.

There have been no controlled trials that have directly assessed the effects of different target oxygen ranges on either short or long-term infant development. In the STOP-ROP trial,[106] there was no difference in the short-term development measures (at 3 months corrected age), assessed as secondary outcomes, between the two groups of preterm infants with pre-threshold ROP randomly allocated to target either SpO_2 89-94% or 96-99%. There is ample observational data (case control and cohort studies) to support the hypothesis that inadequate oxygenation contributes to poor long-term development in preterm/LBW infants with a diagnosis of CLD or BPD.[1, 8, 10, 11, 14-18, 115-120] Outcomes for these infants include increased rates of neurological impairment and significant developmental delay with or without early markers of poor neurological outcome (grade 3 or 4 intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL)).

1.6.5 Sleep patterns

Sleep state disturbances have been frequently reported in infants with chronic oxygen dependency.[82, 83, 121, 122] However, the long-term significance of such disturbances remains controversial as there are no randomised trials that have provided direct evidence that increasing the level of oxygen supplementation improves sleep patterns or other related,

clinically meaningful outcomes. A 1998 case control study found that targeting a SaO_2 of >93% was as efficacious as a SaO_2 >97% in optimising sleep architecture in preterm CLD infants.[123] Other work has suggested that continuing oxygen supplementation during sleep to maintain SpO_2 >97% improves the proportion of time spent in quiet sleep for infants with chronic oxygen dependency.[82,124]

1.6.6 Respiratory system

Physiological studies have consistently demonstrated that preterm infants with lower baseline oxygenation have more frequent and prolonged apnoeic episodes[125-127] and increased oxygen consumption.[79,128-130]

Only physiological and observational studies have been undertaken to assess the effect of oxygen saturation levels on apnoea and hypoxaemia in chronically oxygen dependent preterm/LBW infants. These studies have shown that among infants with increased oxygen requirements, oxygen desaturation during sleep and after feeding can result in hypoxaemia and apnoea.[80,81,124,131,132] These babies spend a greater than average time at "less than adequate oxygen saturation" and have more frequent desaturation episodes,[81,131] although what constitutes adequate oxygenation remains unknown.[133] There has also been some concern that preterm infants needing respiratory support may be maintained at an inappropriately low baseline saturation levels in comparison to non-distressed preterm infants.[29,80,81,134,135] It has been hypothesised that desaturation in these infants could be due to an increase in the frequency of apnoeic pauses in response to airway hypoxia.[30,127] It appeared that both central apnoea and periodic breathing densities decline significantly with improvement in oxygen saturation.[80] An association between subclinical hypoxaemia and respiratory control in preterm infants was demonstrated in a prospective study of 35 infants with CLD throughout their first year of life.[136] A predischarge mean SpO_2 below 90% was identified in eight infants who subsequently had an apparent life-threatening event or died of sudden infant death syndrome (SIDS).

The effects of mild airway hypoxia (FiO_2 0.15-0.16) on respiratory control have been studied in a group of 34 healthy 2-6 month old term infants.[137] Although there was an increase in

periodic breathing, most infants showed only a modest decrease in their baseline SpO_2 during breathing of hypoxic gas mixtures (from median 97.5% to 92.8%). Hypoxia may also cause an increase in airway resistance in infants with CLD,[138] as well as an increased work of breathing.[139] As a result of their study, the latter authors suggested that SpO_2 in infants with CLD should be maintained at 94-96%.

A recent physiological study[82] has shown that continuing oxygen supplementation during sleep in order to maintain $SpO_2 \geq 98\%$ improves respiratory stability in infants with chronic oxygen dependency by reducing desaturations, apnoea and bradycardia. The only randomised trial of differing levels of oxygen therapy in preterm infants (for treatment of pre-threshold ROP)[106] in which pulmonary measures were collected as secondary outcomes found that the higher target SpO_2 range (96-99%) resulted in a significantly increased risk of adverse pulmonary events including pneumonia, exacerbations of chronic lung disease and the need for oxygen, diuretics, and hospitalisation at 3 months corrected age. Several other case control and cohort studies have confirmed that infants with prolonged oxygen dependence have significantly more days of rehospitalisation.[18-22] Long-term follow-up cohort studies have shown conflicting results, with some indicating that subclinical pulmonary dysfunction in children with BPD persists at school age.[140] In contrast, others have found that the exercise capacity of children who had had severe BPD is similar to that of term controls,[141] whilst others have shown that the respiratory health of LBW children at 14 years of age is comparable to that of term controls.[146] It has been suggested that perhaps a more favourable prognosis of pulmonary outcome for extremely low birthweight infants is now warranted.[142]

1.6.7 Cardiovascular system

A non-randomised, crossover trial investigated the effects on oxygenation of targeting a higher (93-96%) versus lower (89-92%) SpO_2 range in low birthweight infants receiving mechanical ventilation in the early neonatal period (median age 42 hours).[143] Although there was a significant difference in the respective oxygen contents (18.0 vs 16.9 ml/dl, P<0.001), there was no change in oxygen consumption or any compensatory increase in cardiac output. The authors concluded that the "low normal" SpO_2 target range allowed for less oxygen exposure without deleterious cardiovascular side effects. Similarly, an uncontrolled study of decreasing

arterial blood saturation from 95% to 90% in preterm infants at a mean age of 61.7 hours, measured changes in echocardiographic indices.[144] This study found that a decrease in SpO_2 did not have any effect on the pulmonary circulatory haemodynamics or the ductus arteriosus.

It is hypothesised that a persistence of inadequate oxygenation beyond term-equivalent age may predispose infants with CLD to pulmonary hypertension.[145-149] Several physiological studies have also demonstrated that infants with CLD may respond to even small changes in oxygenation with significant changes to pulmonary artery pressure (PAP) and/or pulmonary vascular resistance (PVR).[150-152] However, the effects of these cardiovascular changes on clinically important, long-term outcomes have not been demonstrated in randomised trials.

1.6.8 Summary of effects of differing target oxygen levels on outcomes

Despite oxygen being an exceedingly common therapy used on newborn infants, there is surprisingly little direct evidence in the form of randomised controlled trials of the most appropriate ranges to maintain oxygen levels for either term or preterm infants, or a threshold value below which oxygen should be administered. Generally, targeting higher oxygen levels seems to improve short-term outcomes. However, higher oxygen levels have very few demonstrable long-term benefits that can be supported by direct evidence, and may potentially have significant adverse sequelae. The existing evidence in summarised in Table 1.

It was thus necessary to investigate the benefits and harms of maintaining higher versus standard oxygen saturation levels using a randomised controlled trial study design. As noted by Duc and Sinclair (1992, page 194),[25] a high priority for future research should be given to a "comprehensive assessment of the effects of targeting ambient oxygen concentration to achieve a lower vs higher range of PaO_2 (or other index of oxygenation)". Hence it was important to address this research question with a sound and appropriate methodological design,[154] so that this experimental treatment could be evaluated comprehensively, and a real improvement in medical care achieved. Moreover, the lack of direct evidence of the effect of different oxygen levels on clinically meaningful, long-term outcomes has contributed to the wide variation in practice currently seen[86, 155-157] and has fuelled the current controversy surrounding the issue of what are the most appropriate levels of oxygenation for preterm infants.[24, 27, 91, 158-165]

Table 1: Summary of existing evidence regarding effects differing target oxygen levels

System effect	Physiological evidence	Uncontrolled, human observational evidence	Randomised controlled trials (RCT)
Early mortality			87-89 No major effects
Late mortality		91-94 No major effects	90 No major effects
Ophthalmic	102, 110 Suggests adverse effects of higher oxygen targeting	91, 105 Suggests adverse effects of higher oxygen targeting 107-109, 111 Suggests beneficial effects of higher oxygen targeting	87, 95, 103, 104 Suggests adverse effects of higher oxygen targeting 106 No major effects
Early growth		13, 91 Suggests adverse effects of higher oxygen targeting	106 No major effects
Long-term growth		9, 12, 15, 84, 85, 112, 114 Suggests beneficial effects of higher oxygen targeting 113 No major effects	**No RCT evidence**
Long-term neurodevelopment		1, 8, 10, 11, 14-17, 115-120 Suggests beneficial effects of higher oxygen targeting	**No RCT evidence**
Sleep patterns		82, 83, 121, 122, 124 Suggests beneficial effects of higher oxygen targeting 123 No major effects	No RCT evidence
Respiratory	29, 30, 80-82, 125-127, 134, 135, 137-139 Suggests beneficial effects of higher oxygen targeting	18-22, 29, 80, 81, 124, 131, 132, 134-136, 140, 142, 153 Suggests beneficial effects of higher oxygen targeting	106 Suggests adverse effects of higher oxygen targeting
Cardiovascular	150-152 Suggests beneficial effects of higher oxygen targeting	143, 144 No major effects 145-149 Suggests beneficial effects of higher oxygen targeting	No RCT evidence

Numbers indicate reference numbers.

1.7 Hypothesis

The primary hypothesis of this thesis was that maintaining oxygen saturation at a higher level, among babies born at less than 30 weeks' gestation who are oxygen-dependent at 32 weeks postmenstrual age, improves physical growth and neurodevelopment at one year corrected age.

1.8 Aims

The aims of the study were:

1.8.1   to determine whether there was a clinically important difference between the study groups, higher (95-98%) versus standard (91-94%) oxygen saturation targeting ranges, in terms of long-term physical growth and neurodevelopment; and

1.8.2   to determine the benefits and harms of the treatment, as measured by morbidity, mortality and burden to the health care system and families.

1.9 Summary of the project's significance and potential impact

This is the first randomised controlled trial to examine whether maintaining a higher level of oxygen saturation in the blood of chronically oxygen-dependent babies improves growth and development. The study aimed to establish whether a specified higher range of oxygen saturation, as measured by pulse oximetry, was both safe and efficacious.

The benefits of maintaining a higher oxygen saturation level may occur in the form of: an early discharge because of enhanced weight gain and a better respiratory course; a "healthier" infant that is more interactive with parents; weight gain and neurodevelopmental outcomes that are significantly better at one year corrected age; and less frequent rehospitalisations. The costs of maintaining a higher saturation may occur in the form of: an extended hospitalisation because of more time on oxygen; the illness being perceived as more severe by parents and staff; an increase in monetary costs to the health care system and to families; and increased stress on parents if a baby is discharged home on oxygen and the caring role is shifted to parents.

1.10 BOOST acronym

The randomised trial described in this thesis operated under the acronym of the "**B**OOST" trial. This stood for the **B**enefits **O**f **O**xygen **S**aturation **T**argeting trial. The BOOST logo appears on various forms and documents throughout this thesis.

_____

The question under investigation, establishing the benefits and harms of higher oxygen saturation targeting, was studied using the randomised, controlled trial methodology. The detailed methodology of the study design reported as follows conforms to the revised CONSORT statement[166] for the quality reporting of randomised trials.

2.1 Eligibility criteria

2.1.1 Inclusion criteria

- Babies born at less than 30 weeks' gestational age who were oxygen-dependent at 32 weeks postmenstrual age.

- Agreement of parents to participate in long-term follow-up.

- Registration at one of the neonatal intensive care units (NICU) of the eight participating perinatal centres (see Appendix 2).

This gestational age limit was chosen as infants born at less than 30 weeks' gestation are at significantly increased risk of both the clinical problem, prolonged oxygen dependency,[3] and the outcomes to be assessed (see section 2.6).[28] Similarly, the choice of studying infants who remained oxygen-dependent only after 32 weeks pma, rather than an earlier age, was to exclude those infants for whom prolonged oxygen dependency is not a significant clinical problem. Using the current definition of chronic lung disease, oxygen dependency at 36 weeks pma,[4] as the enrolment criterion would have been problematic for two reasons. First, it would have substantially increased the recruitment period as the numbers of eligible, oxygen-dependent infants would have been more than halved from a cohort of 545 eligible infants at 32 weeks pma to only 262 infants being eligible at 36 weeks pma during the recruitment period.[167] More importantly however, it is around 32 weeks pma that extremely preterm infants are emerging from the acute, critical phase of their illness and clinicians are faced with the dilemma of whether to aim the infant's oxygen saturation level higher to maximise potential benefits or target lower levels in order to ensure the infant is discharged home as soon as possible.

The trial was designed to be pragmatic, rather than explanatory,[168] in nature (see section 2.2.2). Hence, there was no requirement for any formal assessment of oxygen dependency, such as an air safety test,[169, 170] in order to fulfill the inclusion criteria. Infants simply needed to be receiving supplementary oxygen, via any mode, in order to be eligible for enrolment. Increasing the complexity of the enrolment procedures would have been a barrier to recruitment.[171]

Prior to 32 weeks pma, some otherwise eligible infants would have already been transferred back to a special care nursery closer to home. It was not logistically possible to approach all these infants, given the trial resources. Hence, only eligible infants who were still in one of the eight participating tertiary neonatal intensive care units were approached for consent. In order to recruit enough infants in a timely manner (see section 2.7.1) the trial needed to be multicentred, which also increased the generalisability of the results by incorporating a spectrum of clinical practice. All eight perinatal neonatal intensive care units in New South Wales (NSW) and the Australian Capital Territory (ACT) were invited to participate and all but one agreed to join. An additional centre from Queensland also joined the collaboration approximately one year after recruitment commenced (see Appendix 2 for the full list of participating centres).

2.1.2 Exclusion criteria

Infants with the following characteristics were not eligible for inclusion:

- lethal and selected congenital defects, including: congenital heart defects; congenital lung defects; intestinal atresias or stenoses; anomalies of the abdominal wall
- major surgery and disease complications influencing growth and development directly, including: intestinal resections/ostomies/fistulas; ventriculostomies; ventricular shunts
- grade 3 or grade 4 intraventricular haemorrhage (IVH), periventricular (cystic) leukomalacia (PVL), porencephalic cyst, or any other established neurological injury or abnormality by 32 weeks postmenstrual age (diagnosed by head ultrasound at enrolment or earlier)
- babies expected to die imminently at the time of eligibility assessment (as determined by the primary clinician)

- babies not expected to live with the biological mother (if adoption was planned or if baby was to live with family other than the biological mother, as noted in medical record or after discussion with clinical staff)
- infants of multiple confinements if more than two infants were eligible at 32 weeks postmenstrual age

Infants with any of the conditions in the first three exclusion categories are known to be at significant risk of poor growth and neurodevelopmental outcomes,[1, 17, 28, 172] the primary study endpoints, and hence they were not included in the trial population even though this may have implications for the generalisibility of the trial's results. The uncertainty arises in otherwise well, extremely preterm infants who remain oxygen-dependent at 32 weeks pma, as to the best approach regarding their oxygen saturation levels in order to maximise benefits whilst minimising harms. We thought it unethical to approach parents of infants expected to die imminently at the time of eligibility assessment and thus they were also excluded. Infants who were not expected to live with their biological mother were also not considered for inclusion as several of the secondary outcomes required information that could only be provided by the infant's mother, such as the Edinburgh Postnatal Depression Scale (see section 2.6.3.4).

We thought that parents of infants from multiple births (e.g. twins) might be reluctant to enter their children in the trial if there was a possibility that the infants might receive different treatments which could potentially result in differing lengths of hospital stay. We anticipated that related multiples, that is more than one eligible infant from one birth, would comprise less than 10% of the cohort. Hence, we thought it both ethical and feasible to randomise only one infant from an eligible pair, and then allocate the second eligible infant to the same treatment group as their sibling (see section 2.2.2). Confinements with three or more eligible infants were not considered for inclusion as this situation would be extremely rare and would pose both ethical and feasibility dilemmas.

2.1.3 Permitted temporary protocol violation

It was necessary to allow temporary protocol violations in situations where higher oxygen targeting was considered established standard practice and where the masking of actual saturation values required by the protocol (see section 2.2.3) would not be appropriate.

Clinicians were encouraged to discuss the need to temporarily withdraw infants from the protocol with the principal investigator (DHS, see Appendix 1) before doing so. Situations or conditions that warranted temporary suspension of the trial protocol included a significant intercurrent illness, surgery, threshold retinopathy of prematurity,[173] or significant abnormalities on polygraphic sleep studies. As soon as possible following the resolution of the situation or condition, the study protocol was resumed. The days and reasons for temporary protocol suspension were documented.

2.1.4 Permanent withdrawal criteria

All attempts were made to keep permanent protocol withdrawals to a minimum. Legitimate reasons for withdrawing an infant from the stud y protocol permanently included parental refusal to continue participation, or at the clinician's request (again following discussion with the principal investigator) if it was believed that remaining in the trial would significantly compromise the infant's clinical state. The reasons and dates of permanent protocol suspension were documented. All withdrawals were maintained in the groups as originally allocated for analysis.

2.2 Study design

2.2.1 Treatments under study

The two study arms consisted of maintaining oxygen saturation levels, using pulse oximetry (SpO_2), at a higher (95-98%) versus standard (91-94%) level. The oximeters used, Nellcor N-3000 Symphonies, calculate oxygen saturation using an algorithm which assesses functional oxygen saturation (see section 1.4).[51, 174] Oximeters which assess fractional saturation, such as the Ohmeda brand, display values approximately 2% below oximeters using a functional saturation algorithm.[52, 53] Both types of oximeter were commonly in use in the participating NICUs at the time of trial recruitment so staff were familiar with their use and operation.

The two SpO_2 levels were chosen as they represented two ends of the spectrum of current accepted clinical practice as assessed by a pre-trial survey of the participating units.[86] Opinion was evenly divided amongst respondents as to which end of the spectrum was most beneficial

with regard to growth and development outcomes, suggesting genuine equipoise regarding the treatment options.

2.2.2 Study type and randomisation scheme

The study design used was a randomised controlled trial as this methodology provides the most reliable evidence of the effects of interventions or treatments, particularly when such effects are moderate.[175] The trial was pragmatic in nature, that is, it was designed to enable a comparison of the two treatments under the conditions in which they would be applied in practice.[168] This approach differs from trials of an explanatory nature that seek to assess the effect of a drug or treatment under "laboratory" conditions rather than how the treatment would be applied in real clinical practice. It is now well recognised that pragmatic trials give clinicians the type of evidence most applicable to their daily practice[175] and this is why this approach was chosen.

Randomisation was stratified using a dynamic balancing method[176] to ensure balance of treatment allocation within hospital, confinement status (singleton/unrelated multiple versus related multiple births) and gestational age (22-27 versus 28-29 weeks) stratum. Singleton births were those with only one infant born per pregnancy. Unrelated multiples were infants born of a multiple pregnancy, but in which by 32 weeks pma only one infant from the birth was eligible for enrolment (the other infant(s) being either ineligible or dead). For the purposes of randomisation, both these types of infants were treated as singletons and were allocated within one randomisation scheme. Related multiples were pairs of eligible infants from the same birth where one infant of the pair was randomised, and the second infant was allocated to the same treatment group as their sibling. Stratification by hospital was used to overcome the potentially confounding effect of differing policies in each of the participating centres with regard to oxygen monitoring, titration and weaning, which may affect secondary outcome measures such as length of hospital stay. Gestational age is known to be highly prognostic of growth and development outcomes[1, 3, 28] so balance of treatment allocation for this factor was considered essential. Pairs of eligible siblings randomised as a single entity were stratified only within hospital strata and not by gestational age strata as the small numbers of such pairs rendered further stratification unnecessary. This was managed by

having a separate randomisation scheme for related multiples in addition to the main scheme for singleton/unrelated multiples. The dynamic balancing method was programmed to allow for a maximal imbalance of 4 or 8 infants per hospital strata (depending on NICU size, categorised as small or large) within the singleton/unrelated multiple randomisation list. The same imbalance limits were allowable for small and large sized NICUs within the related multiple randomisation scheme. These imbalance limits were additive, allowing for an overall maximum imbalance between the treatment groups of 8 in the smaller hospitals and 16 in the larger hospitals.

Concealment of treatment allocation is an important step in ensuring bias is minimised within the randomised trial methodology.[177-179] Allocation concealment in this trial was ensured using the following methods. Randomisation was performed centrally at the National Health and Medical Research Council Clinical Trials Centre during a telephone call from the trial coordinator (LMA, see Appendix 1). Randomisation to either treatment group was registered at the randomisation centre. Reports were provided to the trial statistician (JMS, see Appendix 1) by the NH&MRC Clinical Trials Centre every 3 months regarding recruitment progress and balance within strata, without identifying the treatment allocation of particular infants by ensuring concealment of the actual treatment group. The study oximeter was allocated by the trial coordinator and was only identified as allocated to a particular infant. The research nurses, staff and parents did not know to which treatment group the infant had been assigned.

2.2.3 Blinding procedure

Concealing the treatment group to which the patient has been allocated from the patient (or parents in this case), clinicians and outcome assessors ("double-blinding") if feasible, can reduce both co-intervention and ascertainment bias within a trial.[180, 181] In this trial, double-blinding was achieved using the following method. Randomised infants were assigned a specific study oximeter which, after calculating the infant's saturation in the usual manner, was adjusted to display a value 2% above or 2% below (depending on treatment allocation) the infant's actual saturation. For example, when the *displayed* value was 94%, the *actual* SpO_2 value was either 92% or 96%, depending on the treatment group to which the infant had been allocated (Figure 3).

Staff and parents were then asked to target the infant's SpO_2 in the 93-96% range, thus

blinding them to the actual SpO_2 ranges being targeted. The adjustment was facilitated by the

oximeter manufacturer, Nellcor Puritan Bennett, who produced and installed a specific

research configuration program into each study oximeter which enabled an offset adjustment

of between -5% and +5%.

Figure 3: Mechanism for blinding of treatment allocation

Study oximeter adjusted to display either 2%
above or 2% below infant's actual saturation value
↓
All trial infants target SpO_2 93-96%
using study oximeter

←   →

Actual target range   Actual target range
maintained 91-94%   maintained 95-98%
(2% *below* displayed value)   (2% *above* displayed value)

↓   ↓

Standard group   Higher group
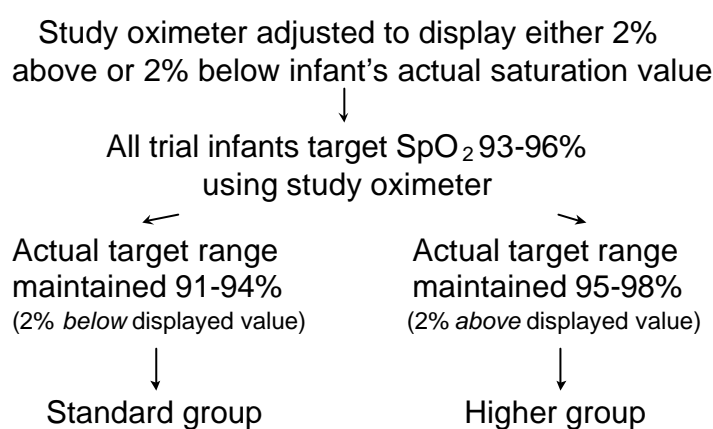
Quality control checks of each oximeter's offset were made every 3 months by the study

coordinator (LMA) using a Nellcor Pulse Oximeter tester (model SRC-2; settings: Light High

1, Modulation Low, RCAL/MODE 63/Local). How each oximeter was offset, either -2% or

+2%, was known only to the trial coordinator. Study oximeters were stored centrally at the

coordinating centre and returned there (by courier or collection by the research nurses) after

each enrolled infant had completed the intervention, ensuring that no participating centre had a

store of study oximeters which might allow local staff to deduce the treatment allocation.

Before the study oximeter was applied to the infant after enrolment, any other form of oxygen

monitoring (including another oximeter or a trancutaneous oxygen monitor) was removed to

prevent unblinding of the study oximeter's offset level. Very few preterm infants beyond 32

weeks pma routinely underwent any other forms of oxygen monitoring, such as intermittent

intra-arterial blood gas measurements, that might also potentially unblind treatment allocation.

Participating institutions agree to keep such interventions to an absolute minimum in trial

infants.

2.3 <u>Recruitment and consent procedures</u>

The institutional ethics committees of the eight enrolment centres approved the trial protocol and the consent forms and information sheets specific to each institution. Annual progress reports were submitted to each ethics committee for the duration of trial recruitment and follow-up. All ethics committees required immediate adverse event reporting.

Designated medical, nursing and data liaison representatives were identified at each enrolment centre to assist with recruitment and consent. These personnel identified eligible infants approaching 32 weeks pma and notified the trial coordinator who kept a log of all infants. Either the liaison representatives, a research nurse or the infant's primary clinician (each participating hospital had preferred personnel for recruitment procedures) then approached the parents or guardians to explain the general outline of the study and invited them to participate in the trial. A parent information sheet (again specific to each centre) was given to the parents (see Appendix 3). Parents were re-approached a few days later and asked whether they would agree to participate in the trial. If they agreed, a signed and witnessed consent form was completed[182] (see Appendix 3). This was photocopied and given to the parents. The original consent form was kept at the coordinating centre, and another copy was placed in the infant's medical record in the NICU.

If the parents were from a non-English-speaking-background, an individual fluent in the parent's language was enlisted for the purposes of interpreting during the consent procedure, and to explain and ensure that the details regarding follow-up were understood. A hospital interpreter or other hospital personnel was engaged to assist in interpreting material, and relatives of parents were only used if suitable personnel were unavailable.

A pager number for study personnel was noted on the consent form. In the first instance, the research nurse fielded all calls related to involvement in the study. If necessary, the principal investigator (DHS) was also available for consultation. Parents were informed both orally and in writing (via the consent and information sheets) that they had the right to withdraw from the study at any time without jeopardising the care of their infant.

It is well recognised in both adult and paediatric trials that the characteristics of participants are often different from those who are eligible, but do not participate in the trial.[183-187] This phenomenon may have implications for the generalisability of the trial results. In order to assess any such effects, a log of eligible but non-enrolled infants was tabulated by the trial coordinator following notification from the liaison representative at each individual centre when an eligible infant was either missed or the parents refused consent. Data regarding several maternal and infant characteristics of all infants born at less than 32 weeks' gestation in NSW and the ACT are routinely collected as part of the NICUS data collection.[188] Permission was sought to access de-identified, summary data of infants within the NICUS data collection who were eligible, but not enrolled in the trial. These summary data were collated at the end of the trial recruitment period.

2.4 Enrolment procedures

At enrolment, but prior to randomisation, several measures were made to determine whether selected exclusion criteria should be applied and this information was recorded on the trial enrolment form (see Appendix 4). The presence or absence of severe intracranial pathology was determined via head ultrasound, done at approximately 31 weeks postmenstrual age to rule out grade 3 or 4 intraventricular haemorrhage, periventricular leukomalacia or porencephalic cyst. The ultrasound was performed by the technician and radiologist who usually performed the procedure and the results were interpreted at each site.

At enrolment, but following randomisation, several measures were made to determine the baseline status for some of the potential confounders and/or adverse outcomes. Maternal depression could potentially confound the primary developmental outcomes.[189, 190] To determine whether maternal postnatal depression scores were distributed equally between the two groups at baseline, the Edinburgh Postnatal Depression Scale (EPDS) was given to the mother for self-completion at enrolment. If a score on the EPDS was higher than 12, then the mother was referred to appropriate psychological and/or psychiatric counselling services as scores above this level are predictive of clinical depression.[191] An elevated EPDS was not a reason to withdraw the family from the study unless the mother and/or the counsellor felt that

this was necessary. An infant eye examination was performed by a paediatric ophthalmologist at the enrolling NICU. Examinations were performed at 32 weeks postmenstrual age. Grading of the severity of ROP was recorded according to the International Classification of Retinopathy of Prematurity.[173] Parents were also asked to self-report several psychosocial factors that may be prognostic for infant growth and development. These included the highest level of parental education, parental height, and maternal age and ethnicity. Information regarding parental occupation, both current and usual, was sought and classified according to the Daniel occupational status scale score.[192]

Once eligibility was determined and informed consent obtained, the study coordinator was contacted and randomisation occurred (see section 2.2.2). The research nurse was then notified of the specific study oximeter to be assigned to each newly enrolled infant. She then facilitated its placement on the enrolled infant as soon as possible either by taking it to the infant's bedside or by having it couriered to centres remote from the coordination centre (such as Newcastle, Canberra and Brisbane). Instructions for oximeter use and the desired (blinded) target range to be maintained were placed prominently near the study oximeter. Brightly coloured "BOOST Trial" stickers were placed on the infant's crib/cot and on the front of the case notes to alert staff that the infant had been enrolled in the trial. These, and other profile raising measures (such as "I'm a BOOST Baby" T-shirts given to the parents after enrolment and at the completion of data collection, see Appendix 5), are recognised methods for promoting a randomised trial.[193]

2.5 Treatment plan

2.5.1 Administration of oxygen

Administration and maintenance of oxygen was managed by the nursing staff and/or parents (in the case of home oxygen). Criteria for titrating or ceasing ambient oxygen were determined by the attending clinicians and not specified by the trial protocol. The blinded target SpO_2 range for all infants enrolled in the study was 93-96% (see Figure 3). Targeting of the allocated saturation range was maintained for the duration of the infant's oxygen need in either a tertiary or non-tertiary nursery, or at home. Prior to any back-transfer of an infant still receiving the trial intervention to a non-tertiary hospital, contact was made with the non-

tertiary nursery staff in order to provide inservice education, equipment and technical support as required. An explanatory letter for the attending clinicians at the back-transfer hospital accompanied each study infant on discharge from the recruiting NICU.

2.5.2 <u>Monitoring of oxygen saturation</u>

The allocated study oximeter was attached to one limb of the infant via a pulse oximeter probe in order to obtain a non-invasive reading of the saturation of haemoglobin with oxygen in arterial blood (SpO_2). The study oximeter was placed next to the infant's cot or crib and displayed the current (blinded) SpO_2 and (actual) heart rate on a screen. The frequency of saturation monitoring, either continuous or intermittent, and specific alarm limit settings were also determined by the attending clinicians and not specified by the trial protocol.

As the trial was pragmatic in nature,[168] assessment of treatment compliance was undertaken only to have some measure of whether, in general, two different treatments were being administered. Thus the purpose of the compliance monitoring was *not* to ensure strict adherence to the protocol as would be required if treatment *efficacy* was being assessed (as in an explanatory trial), but simply to assess compliance with the treatment as it would be administered in actual clinical practice (that is, to measure treatment *effectiveness*).[194] Hence, continuous oxygen saturation monitoring was not considered necessary or appropriate.

SpO_2 measurements for the purposes of monitoring compliance were obtained by collecting 8- (for home oxygen infants) or 24-hour (for in-hospital infants) recordings[195] on a twice-weekly basis whilst the infant remained in hospital and approximately monthly if the infant was discharged on home oxygen. When the research nurse arrived at a neonatal unit for data collection, the previous 8 or 24-hour period of SpO_2 measurements were "downloaded" into a personal computer at the infant's bedside and analysed using computer software (specifically written for the trial's use) that gave a statistical summary of the SpO_2 values. Because vigorous movements can affect the ability of the oximeter to detect the arterial pulse, such artefactual readings were collected but excluded from the compliance analysis.

Results from the downloaded recording were summarised on a printable report which contained a frequency distribution histogram of the blinded saturation values, the median and modal saturation values, the number of valid samples compared with the total number of samples, and the proportion of time the infant had spent in the desired target range over the download period (Figure 4). This information was fed back immediately to nursing and medical staff caring for the infant in order that oxygen therapy could be titrated to comply with the target range if required. A copy of the report was also placed in the infant's case notes for future reference. For satisfactory compliance, the median saturation value and at least approximately 40% of the SpO_2 readings should have been within the blinded 93-96% target range. This information was recorded on a data collection form and entered into the trial database by the research nurses on return to the coordinating centre (see Appendix 6).

Figure 4: Sample download report form
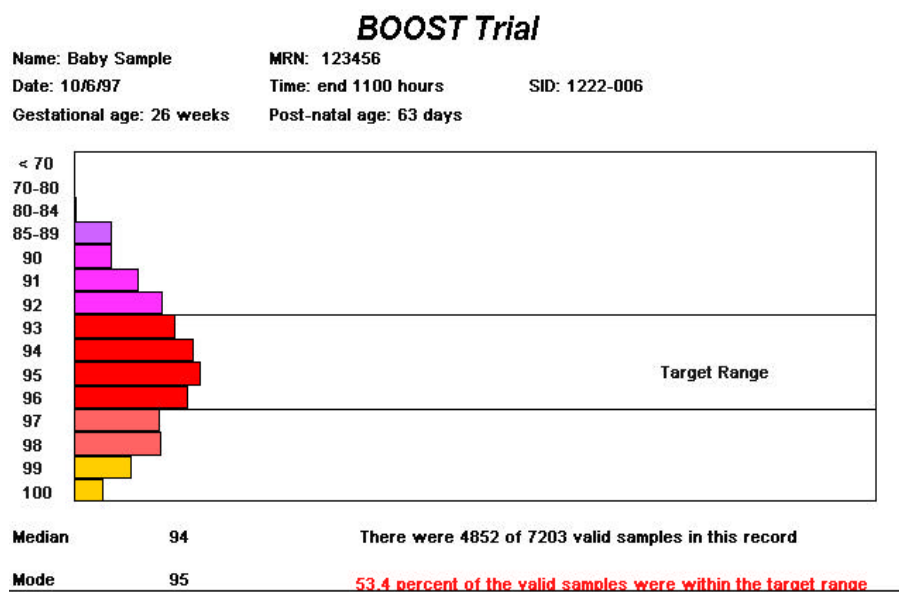
Once the clinicians deemed an infant to be weaned from supplemental oxygen into room air, the designated study oximeter remained at the infant's bedside for one week (or longer, if required). After that time the research nurse collected a final 8 or 24-hour download report with the infant in room air. Again, if the median saturation value and at least 40% of the SpO_2 values fell within the target range, the infant was deemed to have completed the study

intervention and the study oximeter was removed. This procedure was undertaken either in the hospital or the home depending on where the infant was when weaning to air was achieved. If during the first week following weaning to air the infant required further saturation monitoring and/or oxygen therapy, his/her study oximeter (still at the bedside) was used. If, after the return of the study oximeter to the coordinating centre, the infant required further saturation monitoring and/or oxygen therapy in the first year of life, a standard, non-trial oximeter was used. Any such periods of additional supplemental oxygen therapy and/or monitoring were not considered part of the trial intervention.

Monitoring of the degree to which SpO_2 was being kept within the allocated treatment range (unblinded compliance) was managed by the study coordinator. These data and analyses were fedback to the research nurses and clinical staff if remedial action was necessary to improve compliance, while ensuring continued blinding of treatment allocation.

2.5.3 Equipment

Specially adjusted Nellcor N-3000 pulse oximeters were used to ensure blinded targeting of the allocated oxygen saturation range could be achieved (see section 2.2.3).

Oxygen was administered to infants either by nasal cannulae, positioned under the nares and secured to the face with adhesive; headbox with humidification; closed isolette oxygen delivery system; or via a mechanical ventilation circuit as each infant's condition warranted.[196]

Eligibility for home oxygen was determined by the infants' attending clinicians. There was no specific oxygen-dependency test required by the trial protocol.[170] Eligibility criteria for readiness for home oxygen usually included respiratory stability, feeding and weight gain progress and whether the parents were comfortable taking the baby home on oxygen. Oxygen for home use was delivered via cylinders equipped with a flow meter capable of ultra low flow delivery (<3 litres/min) or an oxygen concentrator. Infants receiving home oxygen therapy were managed in conjunction with the usual services provided by their hospital of discharge. This may have included family support nurse visits and follow-up with specialist paediatric respiratory physicians and/or paediatricians.

2.6 Outcome measures

A variety of clinical, psychosocial and health service utilisation information was collected on each infant between enrolment at 32 weeks pma and 12 months corrected age (chronological age plus weeks of prematurity). A schema of the data collection timepoints is illustrated in Figure 5.

Figure 5: Outcome measurement timeline schema
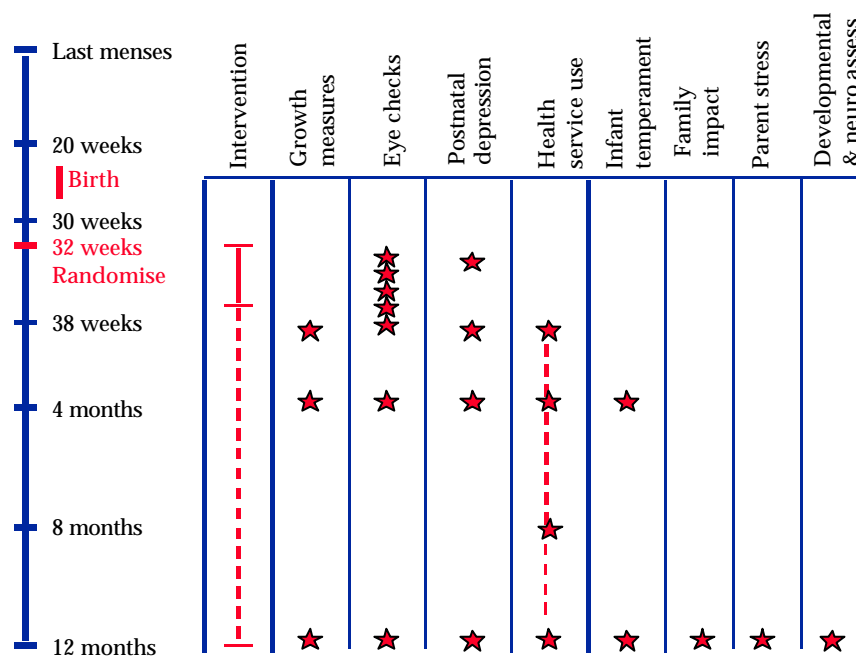
Infants enrolled in the trial had frequent and regular contact with the research nurses in hospital and at home whilst receiving their allocated intervention, primarily during visits to download oxygen saturation compliance information. After supplemental oxygen was no longer required, contact with parents was maintained by the research nurses on a quarterly basis to ascertain health service utilisation data, and determine whether rehospitalisation or death had occurred. This information was confirmed by a combination of parent interview, review of the medical record, contact with the primary general practitioner or paediatrician, and death certificate. In addition, confirmation of current contact details was made to decrease the opportunity for follow-up losses. To improve communication with other providers

regarding study subject participation, a notification sheet identifying the infant as a study participant was placed in the front sleeve of the infant's Personal Health Record booklet (the "blue book") along with the discharge summary.

2.6.1 Baseline measures

The appropriate demographic and clinical variables of each baby were recorded from the medical record using standard clinical definitions. These included: antenatal steroids;[197] gestational age;[71, 72] sex;[73] birthweight;[73] length at birth; head circumference at birth; worst grade intraventricular haemorrhage; 1 and 5 minute Apgar scores; exogenous surfactant treatment;[71] presence or absence of a patent ductus arteriosus;[74] days of assisted ventilation;[74] days receiving parenteral nutrition; episodes of necrotising enterocolitis; maternal ethnicity;[73, 198] parental education, occupation levels and health insurance status;[199] breast versus bottle feeding at discharge;[200] parental heights; and other features of the neonatal course (see Appendix 7). Collection of these data was necessary to establish baseline comparability between the two groups for potential confounders and strong independent predictors of growth and development.

2.6.2 Primary outcomes

2.6.2.1 Growth measures

Growth was measured at three timepoints during the first year of life: at 38 weeks postmenstrual age, and at 4 and 12 months corrected age (see Appendix 8 and Appendix 9). These data were collected either during initial hospitalisation, by the infant's general practitioner, or as part of attendance at a high-risk infant follow-up programme, and were collated by the research nurses. Growth was measured by mean weight, length, and head circumference. An assessment of the proportion of infants small for their age was undertaken by calculating the proportion of infants with weight or length less than the 10th centile, or head circumference less than the 3rd centile.[201]

Growth was measured at these timepoints as this was the usual practice in the participating units. The significance of early growth failure remains controversial with several investigators noting a persistence of poor growth to school age and beyond,[112, 140, 202, 203] whilst more recent

work has suggested that even though very preterm infants are often smaller than expected in early childhood, they show catch-up growth later in life, into adolescence or later.[204, 205] Nevertheless, participating clinicians felt that early growth failure was an important outcome as it may be a marker for later problems.

2.6.2.2 Major developmental abnormality

The proportion of infants in each group with a major developmental abnormality at 12 months corrected age was also ascertained. This was defined as blindness, cerebral palsy or a Revised Griffiths Developmental Scale score more than 2 standard deviations below the mean (general developmental quotient less than 77).[206] Deafness was not included within the definition of major developmental abnormality as it was not considered that differing oxygen saturation target levels would affect this outcome. Blindness was defined as a visual acuity in both eyes of less than 6/60.[207] Cerebral palsy was diagnosed if the child had non-progressive motor impairment characterised by abnormal muscle tone and a decreased range or control of movements accompanied by neurological signs.[208] Infants were assessed using the Revised Griffith's Scale by accredited Griffith's assessors. Such assessors were usually developmental paediatricians or specialist paediatric clinical psychologists. Each recruitment centre had its own high-risk infant follow-up team which included personnel accredited to perform the Griffith's assessments, a follow-up coordinator and usually a paediatric physiotherapist. Seven of the eight follow-up teams involved in the trial had undergone joint Griffith's training but no formal inter-rater reliability assessments were undertaken. If the infant was not able to return to the follow-up clinic connected to the discharge hospital or a clinic of one of the other participating centres, arrangements were made for a regional paediatrician, accredited in Griffith's assessments, to assess the infant if possible. A diagnosis of cerebral palsy was made by the paediatrician examining the infant at 12 months corrected age. Ophthalmic assessments were made by referral of the infant by their follow-up team to local centres skilled in assessing infants born prematurely.

The definition of major developmental abnormality and its assessment methods was standard for extremely preterm infants in the NSW, ACT and Queensland region during the time the trial was undertaken. The Griffiths Mental Development Scale is a well-validated tool for

assessing infant development at one year corrected age.[209] The 1996 revision used in this trial was re-normed using a cohort of British children from the early 1990s, rather than the distribution of developmental quotients based on the original sample of British children from 1954.[206] There are several reasons why the Griffiths Scale is used in this region rather than other scales, such as the Bayley Scales of Infant Development.[210] The primary reason is that the Revised Griffiths Scale looks at development in five different areas including gross motor, personal-social, speech and language, eye-hand co-ordination and performance (general play). A sixth area, practical reasoning, is also measured but this is not part of the assessment until the third year of life. This format allows for a more exact assessment of which areas are causing difficulty for children. The Bayley Scale uses only a motor index and a cognitive index. The Bayley motor assessment combines gross motor and fine motor skills and the mental developmental index mixes play and language. This means that areas of development that are not necessarily developing at the same rate are mixed together in the assessment. For example, if an infant cannot speak or has a specific language delay, an assessment of cognition and other scores are still able to be obtained using the Griffith Scale. Alternatively, if a Bayley scale were used in this situation, once a ceiling on a language item is reached, the scoring is maximised. Moreover, the Griffith Scale can be administered, with good predictive value,[211] into early childhood, making it preferable if longer-term follow-up of the cohort is warranted.

The predictive value of Griffiths assessments at 12 months corrected age in screening for later neurodevelopmental problems is variable. In one study the correlation between the 1 year Griffiths general quotient and 5 year IQ was 0.47,[211] whilst others have found good correlations (correlation coefficient 0.71) between developmental assessments at 1 and 7 years of age[212] suggesting reliable predictive validity for this tool at 12 months corrected age. Developmental status as assessed by the Griffiths scale at 1 year has been shown to be predictive for developmental status at 2 years,[213] the timepoint at which many other studies involving preterm infants usually assess children for major developmental abnormality. It was for these reasons, and the fact that it was usual clinical practice by the participating centres to follow-up these children at 12 rather than 18-24 months, that neurodevelopmental assessment was undertaken in this format.

Similarly, the predictive value of a diagnosis of cerebral palsy at 12 months corrected age is good. 1998 data from the host institution (King George V Hospital) revealed a diagnosis of cerebral palsy at 1 year had a 90% sensitivity and 99% specificity in predicting cerebral palsy at 5 years of age (n=531 children assessed at 1, 3 and 5 years). Others have demonstrated that an early assessment of neuromotor signs has good predictive value for a diagnosis of cerebral palsy.[214-216]

All outcome data collected at 12 months corrected age were recorded on a data collection form (see Appendix 9).

2.6.2.3 Pre-specified sub-group analyses

Two sub-groups were identified *a priori* for supplementary analysis in addition to the full cohort of trial infants. These included infants born at less than 28 weeks' gestation and those infants receiving continuing supplemental oxygen at home after discharge. Both these sub-groups are known to have significantly increased risk of poor growth and development outcomes.[3, 10, 12, 14, 17, 28, 84, 217] It was hypothesised that the experimental treatment, higher oxygen saturation targeting, might be more beneficial in these high-risk sub-groups.

2.6.3 Secondary outcomes

2.6.3.1 Clinical data to discharge

Several secondary outcomes were measured (see section 2.6.3) as it was hypothesised that differing oxygen saturation targeting policies might influence health service utilisation and have cost implications if clinicians were to adopt the experimental treatment of higher saturation targeting as routine practice. The outcomes assessed included: the length of hospital stay (measured in days), in total and after randomisation at 32 weeks pma, and the postmenstrual age at discharge home; the duration of oxygen need, in total and following randomisation (measured in days); the postmenstrual age (measured in weeks) when supplemental oxygen was no longer required; and the duration of assisted ventilation, in total and following randomisation (measured in days). Other outcomes that were considered clinically important were the proportion of infants who remained oxygen dependent at 36 weeks pma and the number of infants receiving home oxygen in each group. The proportion of infants receiving post-natal corticosteroids and diuretics was also assessed as these outcomes

may be indicators of the pulmonary effects of higher oxygen targeting. Prior observational evidence[13] suggested that infants targeted at a higher oxygen saturation level feed better, hence the postmenstrual age at which full sucking feeds was achieved was also assessed and compared between the two groups.

2.6.3.2 Deaths

There was a potential that differing oxygen saturation targeting ranges might either improve or adversely affect the number of deaths occurring after randomisation and up to one year corrected age.[92, 93] Deaths were ascertained by notification from the parents or enrolment hospital. The causes of deaths were classified by ICD-9 code[218] and confirmed by hospital discharge summary, postmortem and/or coroner's report or death certificate. The postmenstrual age at death and whether the death occurred in hospital or at home were also recorded (see Appendix 10).

2.6.3.3 Ophthalmic outcomes

Retinopathy of prematurity (ROP) was assessed by routine, standardised ophthalmic examinations by a paediatric ophthalmologist at two-week intervals from enrolment until resolution, treatment or stabilisation of the condition. Grading of the severity of ROP was recorded according to the International Classification of Retinopathy of Prematurity[173] (see Appendix 11). The worst stage of ROP and whether ablative retinal surgery treatment for threshold ROP was required were documented as severe ROP, with or without retinal surgery, is associated with unfavourable visual outcomes.[97, 99, 219] Infants with severe ROP (stage 3 and above) underwent an eye examination at 12 months corrected age to assess major ophthalmological outcomes and visual acuity.

2.6.3.4 Psychosocial outcomes

It was hypotheised that higher oxygen saturation targeting might result in a "healthier" and thus more interactive infant during the first year of life. Conceivably this might also reduce postnatal depression rates, parental stress and the impact an extremely preterm infant has on the family unit. However, if higher oxygen targeting resulted in more days in both oxygen and

hospital, and/or increased the risk of home oxygen, these events might have adverse effects on the infant's temperament, the parents and the family as a whole. It is well established that maternal depression and parenting stress can adversely affect long-term cognitive development in children.[189, 190, 220-222] To assess these potential effects, several well-validated scales were administered during the first year of life. The scales were given to the mother at either the enrolment hospital or another centre where the follow-up visit took place. If this were not possible, the forms (with a letter of explanation) were posted to the family. They were returned by reply paid mail. The use of postal questionnaires to assess trial outcomes in this population of infants has been shown to be valid.[223]

The Edinburgh Postnatal Depression Scale (EPDS) (see Appendix 12) was administered longitudinally to determine whether any changes occurred over time as a result of the infant being allocated to the standard or higher oxygen saturation target ranges. The EPDS was administered at four timepoints: upon enrolment at 32 weeks pma, at 38 weeks pma, and at 4 and 12 months corrected age. The EPDS is a simple, widely used and well-validated screening tool for assessing depressive symptoms in the postnatal period.[191] It has been validated within an Australian population[224] and has been used on mothers following preterm birth.[225]

The 1978 revision of the Infant Temperament Questionnaire[226, 227] was used to assess differences in temperament in infants at 4 months corrected age (see Appendix 13). This questionnaire has also been validated in an Australian sample[228, 229] and in preterm infants.[230] A further development of this scale, the Toddler Temperament Questionnaire,[231] was used to measure temperament in trial participants at 12 months corrected age (see Appendix 14). Again, this tool has been well validated[232] and used in populations of Australian children.[233]

Two further scales were administered at 12 months corrected age in order to assess the impact of the two treatments on the infants' families. The Impact on Family Scale (see Appendix 15) was developed to assess the impact of childhood illness on a family[234] and has been used in cohorts of very low birth weight infants.[235, 236] The short form of the Parenting Stress

Index[237, 238] (see Appendix 16) was chosen to assess parental stress as it has been validated in both parents of children with chronic illness[239] and those with very low birthweight infants.[240]

2.6.3.5 Health service utilisation

It was hypothesised that higher oxygen saturation targeting might result in a "healthier" infant who used health care services less often after discharge.[241-244] Conversely, it was also plausible that higher oxygen saturation targeting might result in increased rates of infants on home oxygen, which could in turn result in an increase in health care service usage.

To assess any differences between the two groups, self-report of health service usage during the first year of life was ascertained by a combination of quarterly phone interview with the parents by the research nurses, review of the medical record and contact with the primary general practitioner or paediatrician. Information was also gathered on categories of provider (general practitioners, routine hospital follow-up visits, early childhood centre visits, nurse home visit, private paediatrician appointments or hospital emergency room / outpatient departments visits) and the reason for the visit (routine, specific illness or developmental therapy) as each of these ha s quite different associated costs (see Appendix 17).

2.6.3.6 Rehospitalisations

Similarly, it was hypothesised that higher oxygen saturation targeting might result in less frequent rehospitalisations in the first year of life.[18-20, 22, 23, 245, 246] Data were collected prospectively on the number, postmenstrual age at readmission, duration and reason for rehospitalisation episodes during the first year of life. Self- report by the parents was confirmed by accessing the infant's medical record. The reasons for admission were categorised as either for respiratory illness, surgery, neurological problems, social problems or for other reasons. The diagnosis related group (DRG) categories[247] assigned to each readmission were obtained along with information about whether the infant had needed admission to an intensive care unit (ICU) and/or required mechanical ventilation during each readmission (see Appendix 18).

2.7 <u>Statistical issues</u>

2.7.1 <u>Sample size and power calculations</u>

2.7.1.1 <u>Baseline risk estimates</u>

To determine an appropriate sample size, data were used from the follow-up programme at the host institution (King George V Hospital) for the year prior to trial commencement, 1995. This analysis was restricted to infants with the same inclusion and exclusion criteria as the trial. The standard oxygen saturation range during this period for such infants was a SpO_2 target of 91-94%, hence the outcome rates reflect the trial control population. Approximately 47% of 1995 King George V infants who would have been eligible for the trial had a weight less than the 10th centile at one year corrected age, and 24% had a major developmental abnormality.

2.7.1.2 <u>Anticipated effects, power and sample size calculations</u>

Sample size was calculated to detect clinically important effects on the primary outcomes that if seen may convince clinicians to change their practice. This included a reduction in the proportion of infants with weights less than the 10th centile at 12 months corrected age from the baseline estimate of 47% to 30%; and a reduction of the major developmental abnormality rate from 24% to 10%. To achieve 80% power, with a 2-sided 0.05 significance level and a 1:1 subject ratio, a sample size of approximately 150 subjects in each arm was required. A total sample size of approximately 300 infants would also have the statistical power to detect clinically important differences in several other primary and secondary outcomes (see Appendix 19 - includes control data from several reference populations). The size of the treatment effect was important because it relates to the clinical importance of the effect.[248] Determining the minimal important difference was determined by asking clinical colleagues what they thought constituted a clinically meaningful difference in outcome rates.[249-251] Sample size calculations were undertaken using the SAM 2.1 sample size calculator (Glasziou, 1992) which calculates sample size based on the differences between two proportions or two means. For proportions, SAM 2.1 uses an iterative method for Walter's arcsine transformation with a continuity correction.[252]

2.7.1.3 <u>Anticipated participation and follow-up rates</u>

The eight participating enrolment centres were of varying sizes and hence a different number
of enrolments from each institution was expected, ranging from 8 to 24 infants per year, with a
total of approximately 124 eligible infants per year expected to be available for recruitment. A
90% participation rate and a 90% follow-up rate was anticipated based on other trials
successfully completed at the participating centres. To allow for a 90% followup rate, the
target sample size to be enrolled was 333 (= 300/0.9). With a 90% participation rate,
approximately 111 (= 124 x 0.9) infants per year were expected to be recruited.

2.7.1.4 <u>Anticipated timeline</u>

Based on the expected numbers and participation rates, the anticipated recruitment period was
3 years (111 x 3 = 333) with a further one year required for the completion of the primary
outcome data collection (see dashed line in Figure 6).

Figure 6: Numbers of infants recruited during the enrolment period
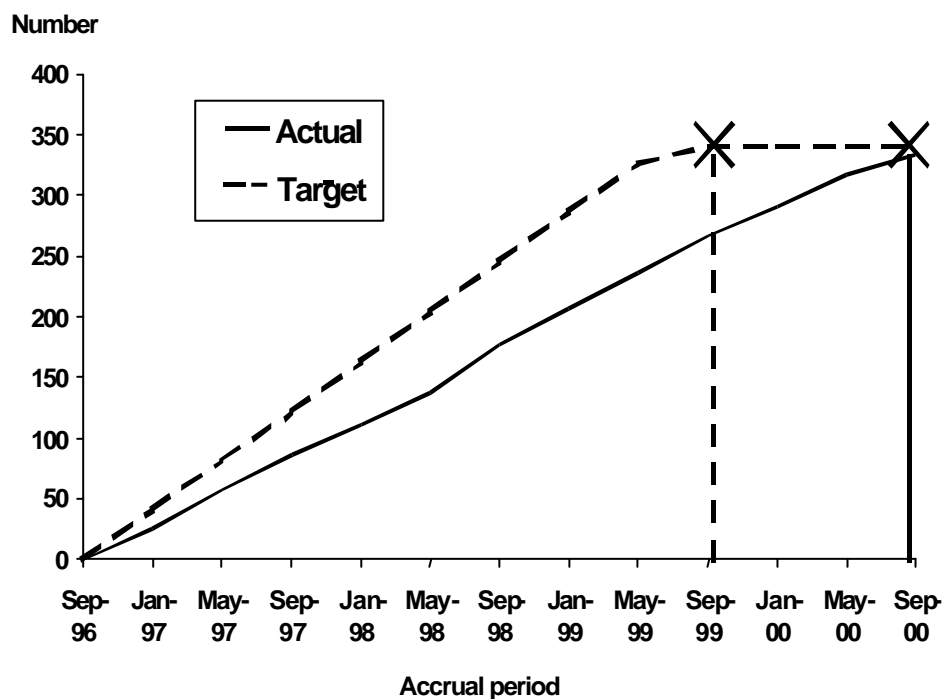
2.7.2 <u>Database management and data storage</u>

Data were entered into a Microsoft ACCESS 2000 database for data management purposes. This database had levels of security allowing the trial coordinator access to all features of the patient record, whilst all other trial personnel were restricted to data fields that did not reveal the infant's treatment allocation. All electronically entered data were stored on a password protected network which was routinely backed-up nightly. Hard copies of data forms were stored in filing cabinets at the coordinating centre which were locked when not in use by the trial staff. Secure disposal of paper data was available through the use of a shredding machine. Electronic data will be disposed of by erasure from floppy disks and hard disks. Data will be kept securely for seven years, as recommended by the NH&MRC. No identifying data were revealed to any person not directly involved with the trial. Trial results will be published in summary format so participants will never be individually identified.

2.7.3 Analysis methods

The statistical analysis was performed using Statistical Analysis System (SAS) software, version 8.2. All data analyses were performed on the groups as originally allocated (intention-to-treat analysis). This included temporary and permanent withdrawals and infants lost to follow-up where data were available.

For continuous data the treatment effect was calculated as the higher target range group minus the standard target range group, with results presented as either means with standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for non-normally distributed data. Data were assessed for skewness and if this was greater than 1 or less than -1, non-normal data analysis methods were used. An assessment of significant differences between the two groups was undertaken using Student's t test or the Mann-Whitney U test and expressed as mean or median differences respectively with 95% confidence intervals. Median differences were calculated in SAS using the Moses macro provided by the SAS Institute. For categorical data the chi square test was used and the treatment effects were expressed as relative risks (RR) of the higher group compared to the standard group, with 95% confidence intervals. When appropriate, the number-needed-to-treat

(NNT) was calculated as the inverse of the absolute risk difference (the event rate in the treatment group minus the event rate in the control group). All P values were two-sided and were not adjusted for multiple testing or correlation between outcomes of siblings. A sensitivity analysis was undertaken to test the effect of the inclusion of sibling pairs on the major outcomes by randomly removing half of the related multiples (see section 2.2.2 and Table 4) from the analysis of these outcomes.

Adjustment for known prognostic factors in this cohort of infants (gestation, gender, ethnicity and plurality)[28] was undertaken, using multiple or logistic regression models, on several secondary clinical outcomes (length of hospital stay and days of mechanical ventilation after randomisation, pma to full sucking feeds, pma at discharge home, and worst stage of ROP) that were expected to show differences between the two oxygen target range groups. Although not strictly necessary in the analysis of randomised trial results, particularly if there are no imbalances in baseline factors that relate to outcomes,[253] such secondary analyses may help achieve peace of mind.[254] As the trial was pragmatic in nature,[168] it was not deemed necessary to undertake compliance adjusted analyses as the aim of the trial was to assess which of the two oxygen saturation ranges was more effective in actual clinical practice.

Review Manager 4.1 software (Cochrane Collaboration, Update Software) was used to produce the boxplots illustrating the main outcome results. The meta-analyses of major outcomes by enrolment centre were also undertaken using Review Manager 4.1, using Mantel-Haenszel methods for combining individual centre results and fixed effects models.

2.8 Safety monitoring committee

2.8.1 Background

As the treatment under investigation, higher oxygen saturation targeting, might potentially have both beneficial and harmful effects, it was considered important that an independent safety monitoring committee (SMC) be included in the trial design.

The composition and numbers suggested for membership of a SMC are somewhat variable. A review of the operational aspects of safety monitoring committees by Hawkins[255] found that

for multicentre trials sponsored by the National Eye Institute, the average number of members was ten. However, a minimum of three members and an odd number of total members (to achieve internal decisions) has been suggested by Pocock.[256] The roles and positions may depend on the subject under study, and in the Hawkins review, a third of the positions were represented by statisticians and another third by ophthalmologists (which would probably translate into clinical specialties relevant to the research question). The recommended number of meetings held and the timing of meetings during the progress of a study again depend on the objectives and responsibilities of the SMC. For example, a fixed and pre-specified number of examinations of the data or *ad hoc* examinations based on the number of events accruing may be utilised. Monitoring for efficacy, safety and data quality in combination or alone are the most frequent purposes of a SMC.[257]

2.8.2 Objectives

The objectives of the trial's SMC were to monitor for specified adverse outcomes in the interest of safety, and to follow trends in the occurrence of other adverse outcomes and unanticipated side effects. A secondary objective was to make recommendations to the principal investigators (DHS, LI, JMS), as a result of examining the data, to ensure the ethical conduct of the study.

2.8.3 Membership

The SMC comprised three people: a paediatric ophthalmologist, a neonatologist and a paediatric respiratory physician who was also an epidemiologist. These appointed members had voting status but none had a direct interest in the results of the study. None of the appointed members had investigator status or was employed by any of the centres participating in the trial.

2.8.4 Analysis timepoints

There were five pre-specified analysis timepoints: at 5 months after the first enrolment (to check that data could be managed efficiently and submitted in a manner appropriate for the SMC), then again after 75, 150, 225 and 300 patients had been enrolled.

2.8.5 Adverse outcomes monitored

There were two major adverse outcomes that might conceivably be affected by differing oxygen saturation target ranges after 32 weeks postmenstrual age: retinopathy of prematurity and mortality. Hence, the outcomes assessed by the SMC were stage 3 or 4 ROP (the more severe stages with significant long-term sequelae) and mortality to 38 weeks pma. Both outcomes were assessed as previously described (see sections 2.6.3.2 and 2.6.3.3).

2.8.6 Stopping rules

The O'Brien Fleming rules for multiple testing[258] were used. If the difference in proportions of ROP stages 3/4 or mortality to 38 weeks pma between the standard and higher group at any evaluation was statistically significant at a 2-sided P value of 0.01 then the SMC could recommend that the trial be stopped. The stopping rules were never breached and the trial was permitted to proceed on each occasion.

2.8.7 Presentation and reporting of data

The trial coordinator (LMA) provided the SMC with the appropriate outcome data in a manner that ensured members of the committee assessed the outcomes masked to treatment group labels. The summary findings and the decision regarding continuation of the trial were reported to the trial coordinator by the SMC chairperson via a written, signed report within two weeks of each meeting (see Appendix 20).

3.1 Participants

3.1.1 Enrolled infants

Figure 7 shows the flow of infants eligible, assigned and followed-up throughout the trial. 358 infants were enrolled: 178 infants were allocated to the standard target range group (SpO$_2$ 91-94%) and 180 to the higher target range group (SpO$_2$ 95-98%). Of these, 333 infants were individually randomised (167 to the standard group and 166 to the higher group) and a further 25 eligible infants (11 and 14 in the standard and higher groups respectively) were allocated to the same treatment as their enrolled sibling.

Figure 7: Numbers of infants screened, enrolled and for whom follow-up data available

703 infants born < 30 wks GA, still O$_2$ dependent at 32 wks pma

158 not eligible:
  lethal congenital abnormalities (n=59)
  major surgery < 32 wks pma (n=21)
  grade 3 or 4 IVH / PVL / cystic lesions
      < 32 wks pma (n=78)

545 infants eligible

187 eligible infants not enrolled:
  no consent (n=122)
  not approached (n=65)

358 infants enrolled

178 infants allocated to the
standard target range group
SpO$_2$ 91-94%
- 167 individually randomised
    (133 singletons, 23 unrelated
    multiples, 11 related multiples)
- 11 related multiples allocated with siblings

180 infants allocated to the
higher target range group
SpO$_2$ 95-98%
- 166 individually randomised
    (129 singletons, 23 unrelated
    multiples, 14 related multiples)
- 14 related multiples allocated with siblings

Primary outcome data available for 166 infants (93%)

12 infants lost to follow-up (n=7) or dead (n=5) (7%)

12 infants lost to follow-up (n=3) or dead (n=9) (7%)

Primary outcome data available for 168 infants (93%)

Randomisation resulted in prognostic baseline infant and maternal characteristics being well balanced between the two groups (see Table 2). The mean gestational age of enrolled infants was 26.5 weeks (SD 1.7) and the mean birth weight was 917 grams (SD 229). 73% of infants were singleton births and 94% of infants were born in a tertiary hospital with NICU facilities. 83% of the mothers received at least some antenatal corticosteroids prior to delivery. This profile of the circumstances surrounding the birth of extremely preterm infants is typical of current perinatal practice in Australasia.[28] Similarly BOOST trial infants experienced the myriad of interventions and conditions that typify modern NICU care.[28] This included 77% receiving endogenous surfactant, 16% receiving high frequency ventilation, and experiencing a median of 12 days (IQR 4-28) of mechanical ventilation via an endotracheal tube. The enrolled infants required a median of 13 days of total parenteral nutrition (TPN), 86% required active treatment for apnoea and bradycardia and 52% suffered a patent ductus arteriosus (PDA). Six infants (3 in each group) had a diagnosis of severe intracranial pathology after 32 weeks postmenstrual age, despite this being a pre-randomisation exclusion criteria.

Randomisation also helped overcome the potentially biasing effects of imbalances between the two groups for factors in addition to the infant's health status. All the self reported physical, socio-economic and psychosocial factors such as parental height, ethnicity, education, occupation and depression were well balanced between the two groups at enrolment (see Table 2). Significance tests for baseline differences are in appropriate[178, 254, 259, 260] and were thus not undertaken.

3.1.2 Non-enrolled infants

During the 4 year recruitment period, there were 703 infants who were born at less than 30 weeks' gestation and remained oxygen-dependent at 32 weeks pma. Of these, 158 fulfilled one or more of the exclusion criteria and were thus not eligible for enrolment.[188] The reasons for exclusion are listed in Figure 7. After pre-randomisation exclusions, there were 545 eligible infants potentially available for recruitment. Of these, 187 infants were eligible but not enrolled, hence 66% (358/545) of eligible infants were actually recruited to the trial. For 122 of these infants the reason for non-enrolment was refusal of parental consent. This 22% (122/545) refusal rate is similar to that reported in other clinical trials where eligible patient logs are kept.[261-263]

Table 2: Baseline infant and parental characteristics of enrolled infants

Variable	SpO$_2$ 91-94% Control group N=178	SpO$_2$ 95-98% Treatment group N=180	Both groups N=358
Gestational age	26.6 weeks (SD 1.7)	26.5 weeks (SD 1.6)	26.5 weeks (SD 1.7)
Male gender	92 (51.7%)	97 (53.9%)	189 (52.8%)
Birth weight	917.8 grams (SD 228.5)	916.4 grams (SD 230.6)	917.1 grams (SD 229.3)
Birth wt <10th centile	14 (7.9%)	21 (11.7%)	35 (9.8%)
Birth head circumference	24.6 cm (SD 2.0)	24.6 cm (SD 2.2)	24.6 cm (SD 2.1)
Birth length	35.6 cm (SD 4.1)	35.3 cm (SD 4.0)	35.5 cm (SD 4.1)
Singletons*	133 (74.7%)	129 (71.7%)	262 (73.2%)
5 min Apgar score <7	31 (17.4%)	37 (20.6%)	68 (19.0%)
Born in tertiary hospital with NICU	163 (91.6%)	172 (95.6%)	335 (93.6%)
Surfactant	138 (77.5%)	137 (76.1%)	275 (76.8%)
PDA	94 (52.8%)	91 (50.6%)	185 (51.7%)
Apnoea/bradycardia requiring treatment	157 (88.2%)	149 (82.8%)	306 (85.5%)
Days TPN	13.5 days (IQR 9-20)	13.0 days (IQR 9-20)	13.0 days (IQR 9-20)
No NEC	167 (93.8%)	170 (94.4%)	337 (94.1%)
Worst IVH Grade 3, 4 or PVL	3 (1.7%)	3 (1.7%)	6 (1.7%)
Days mechanical ventilation (via ETT)	12.0 days (IQR 4-28)	13.0 days (IQR 4-28)	12.0 days (IQR 4-28)
HFV	28 (15.7%)	28 (15.6%)	56 (15.6%)
Antenatal steroids (any)	148 (83.2%)	149 (82.8%)	297 (83.0%)
Maternal tertiary education	60 (33.7%)	64 (35.6%)	124 (34.6%)
Paternal tertiary education	73 (41.0%)	65 (36.1%)	138 (38.6%)
Mother's usual occupation score	4.5 (SD 1.4)	4.6 (SD 1.3)	4.5 (SD 1.4)
Father's usual occupation score	4.4 (SD 1.4)	4.7 (SD 1.3)	4.5 (SD 1.3)
Mother's height	163.2 cm (SD 7.3)	162.7 cm (SD 7.6)	162.9 (SD 7.5)
Father's height	177.0 cm (SD 8.0)	176.1 cm (SD 8.7)	176.5 (SD 8.4)
Mean EPDS at entry	10.7 (SD 5.7)	10.0 (SD 5.3)	10.4 (SD 5.5)
Proportion with EPDS > 12 at entry	46 (33.3%, N=138)	42 (31.3%, N=134)	88 (32.4%, N=272)
Maternal age (years)	29.99 (SD 6.0)	29.47 (SD 6.1)	29.7 (SD 6.1)
Maternal ethnicity Caucasian	148 (83.2%)	141 (78.3%)	289 (80.7%)

NICU	- neonatal intensive care unit	* Singletons = births with only one fetus,
PDA	- patent ductus arteriosus	not including "unrelated multiples" (see Table 4)
TPN	- total parenteral nutrition	
NEC	- necrotising enterocolitis	
IVH	- intraventricular haemorrhage	
PVL	- periventricular leukomalacia	
ETT	- endotracheal tube	
HFV	- high frequency ventilation	
EPDS	- Edinburgh Postnatal Depression Scale score	

The main reason (n=38) for refusal of consent was that by 32 weeks pma, when the infant had been in hospital for 3-10 weeks since birth, many parents felt that they "did not want to change things", that their baby had reached a stable period and they were reluctant to change to the use of a different oximeter which was required to ensure blinding of treatment allocation. Relatively few parents (n=9) refused consent because of concerns regarding potentially too much or too little supplemental oxygen or because they were unwilling to participate in research projects. No parents cited concerns regarding the fact that the study oximeters displayed *adjusted*, rather than *actual*, values to ensure blinding of treatment allocation (see section 2.2.3) as the reason for refusing consent. The main reason (57/65) that eligible infants were not approached to participate was that the parents were infrequent visitors and were unable to be contacted prior to 32 weeks in order to seek informed consent. Only 4 eligible families were not approached due to lack of English fluency and the non-availability of an appropriate interpreter.

An analysis of the summary, de-identified NICUS data[188] of the 187 eligible but non-enrolled infants revealed no *clinically* important differences in their baseline infant or maternal characteristics compared with the 358 eligible and enrolled infants (see Table 3), despite the non-enrolled infants being slightly heavier at birth and of 0.7 weeks greater gestation.

Table 3: Baseline infant/maternal characteristics of non-enrolled and enrolled infants

Variable	Non-enrolled infants N=187	Enrolled infants N=358	P value
Gestational age	27.2 weeks (SD 1.5)	26.5 weeks (SD 1.7)	P<0.00001
Male gender	105 (56.2%)	189 (52.8%)	P=0.5
Birth weight	1016.3 grams (SD 249.9)	917.1 grams (SD 229.3)	P<0.00001
Birth head circumference	25.4 cm (SD 2.2)	24.6 cm (SD 2.1)	P=0.00004
Singletons	141 (75.4%)	262 (73.2%)	P=0.6
5 minute Apgar score <7	33 (17.7%)	68 (19.0%)	P=0.7
Born in tertiary hospital with NICU	173 (92.5%)	335 (93.6%)	P=0.6
Surfactant	137 (73.3%)	275 (76.8%)	P=0.4
PDA	95 (50.8%)	185 (51.7%)	P=0.8
Days TPN	14.0 days (IQR 9-22)	13.0 days (IQR 9-20)	P=0.3
No NEC	175 (93.6%)	337 (94.1%)	P=0.8
Days mechanical ventilation (via ETT)	7.0 days (IQR 3-18.5)	12.0 days (IQR 4-28)	P=0.01
HFV	20 (10.7%)	56 (15.6%)	P=0.12
Antenatal steroids (any)	169 (90.4%)	297 (83.0%)	P=0.01
Maternal age (years)	29.1 (SD 6.2)	29.7 (SD 6.1)	P=0.3
Maternal ethnicity Caucasian	154 (82.4%)	289 (80.7%)	P=0.6

3.1.3 <u>Recruitment centres</u>

The recruitment centres were of varying sizes, with the numbers enrolled at each centre ranging from 8 to 77 (Figure 8). The numbers of infants allocated to each gestational age stratum, within each institution were well balanced (Table 4) and within the allowable imbalance limits nominated within the dynamic balancing stratification programme (see section 2.2.2).[176] The participating centres recruited at an average rate of 84% of their expected number of enrolments. This resulted in the recruitment timeline increasing from the expected 3 years to 4 years in total, from 16 September 1996-15 September 2000 (see Figure 6).

Figure 8: Numbers of subjects recruited at each participating centre
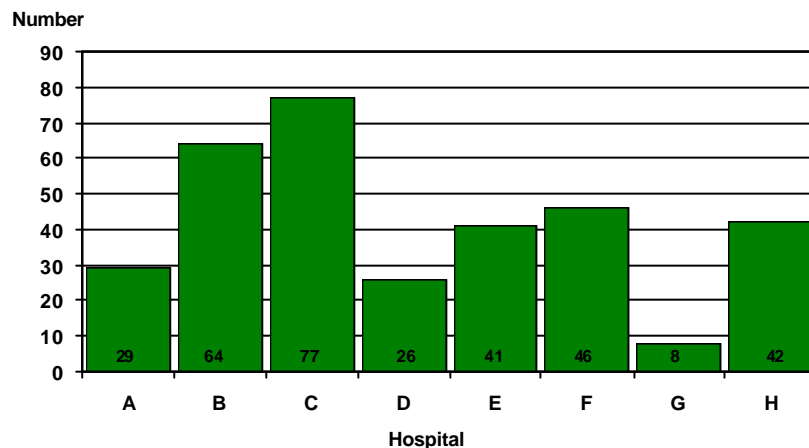
3.2 <u>Intervention</u>

3.2.1 <u>Commencement</u>

Trial coordination measures to ensure timely randomisation appeared to be successful, with the median postmenstrual age at randomisation being 32.0 weeks (IQR 31.6-32.3) as specified in the trial protocol. There was no difference between the two groups in age at randomisation: 32 weeks pma (IQR 31.7-32.3) for the standard target range group and 32 weeks pma (IQR 31.6-32.4) for the higher target range group.

3.2.2 <u>Duration</u>

The intervention, allocation to either oxygen saturation target range, continued for a median of 17.5 days (IQR 7-41) in the standard group and 40 days (IQR 20.5-73) in the higher target range group (P<0.0001), with only 2% (n=7: 1 in the standard group, 6 in the higher group) of enrolled infants still requiring supplemental oxygen at 12 months corrected age.

Table 4: Numbers enrolled in each gestational age stratum, by hospital

Hospital	Gestational age strata	SpO₂ 91-94% N=178	SpO₂ 95-98% N=180	Total N=358
Singletons or unrelated multiples*				
Canberra Hospital	22-27 weeks	9	10	19
	28-29 weeks	6	3	9
John Hunter Hospital	22-27 weeks	18	16	34
	28-29 weeks	11	11	22
King George V Hospital	22-27 weeks	26	26	52
	28-29 weeks	10	11	21
Liverpool Hospital	22-27 weeks	11	9	20
	28-29 weeks	1	2	3
Mater Mothers' Hospital	22-27 weeks	11	14	25
	28-29 weeks	8	6	14
Nepean Hospital	22-27 weeks	18	16	34
	28-29 weeks	5	4	9
Royal Hospital for Women	22-27 weeks	2	2	4
	28-29 weeks	1	2	3
Royal North Shore Hospital	22-27 weeks	13	15	28
	28-29 weeks	6	5	11
Sub total		**156**	**152**	**308**
Related multiples+				
Canberra Hospital	not stratified	0	2	2
John Hunter Hospital	not stratified	8	8	16
King George V Hospital	not stratified	2	6	8
Liverpool Hospital	not stratified	4	2	6
Mater Mothers' Hospital	not stratified	4	0	4
Nepean Hospital	not stratified	2	4	6
Royal Hospital for Women	not stratified	0	2	2
Royal North Shore Hospital	not stratified	2	4	6
Sub total		**22**	**28**	**50**
Total		**178**	**180**	**358**

* **Singleton** = one infant per birth; **unrelated multiple** = from a multiple birth, but by 32 weeks pma only one infant of the birth was eligible for enrolment (other infant(s) either ineligible or dead). For the purposes of randomisation, both these types of infants were treated as singletons.

+ **Related multiple** = pair of infants from the same birth: one infant of the pair was randomised, the second infant was allocated to the same treatment group as their sibling. Actual numbers are indicated in this table.

3.3 Protocol adherence

3.3.1 Incorrect treatment allocation

Upon return of each study oximeter to the coordinating centre after treatment cessation, the oximeter adjustment offset (and thus the actual saturation range targeted) was checked by the trial coordinator. One infant was assigned the incorrect study oximeter at randomisation and was thus not targeted at the allocated range.

3.3.2 Distribution of blinded saturation values targeted

Recording of the blinded median saturation value of each download by the research nurses (see section 2.5.2 and Appendix 6) allowed a comparison of the distribution of these values between the two groups. Figure 9 shows the percentage of downloads in oxygen (n=1,913 download files) with various median saturation values. This confirms that the blinding procedures were successful as both groups targeted the same distribution of blinded saturation values and both groups had the same blinded median SpO_2 value of 95%.

Figure 9: Distribution of blinded saturation values targeted
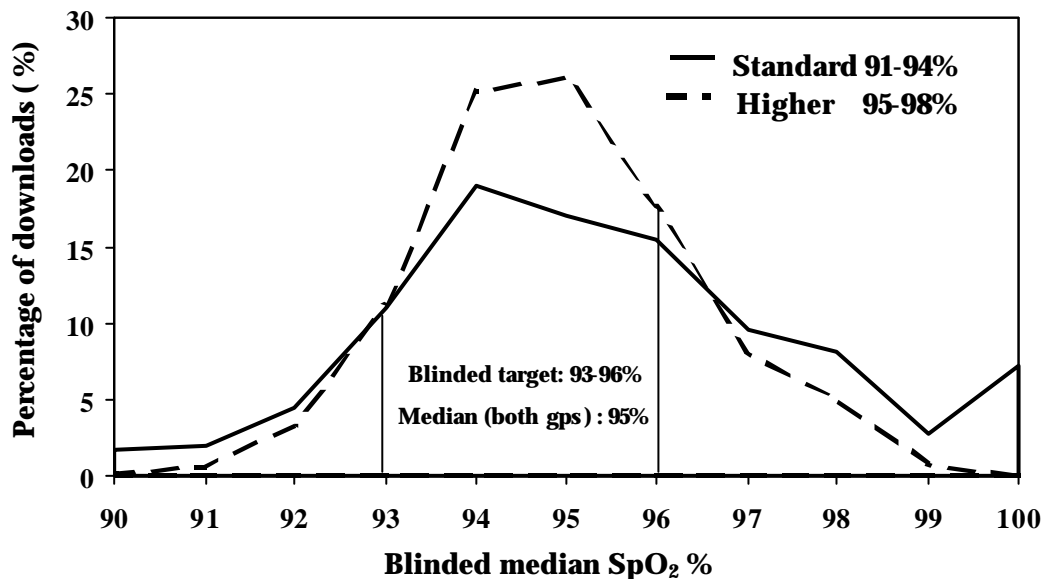
3.3.3 <u>Distribution of actual saturation values targeted</u>

There were 1,913 downloads of 8-24 hours duration done on trial infants whilst they were receiving supplemental oxygen following randomisation. During these download recordings, actual (not blinded) oxygen saturation values were sampled every 10 seconds (see section 2.5.2 for detailed description). This resulted in 14,432,319 data points being available to assess protocol adherence. When these data were analysed the distribution of actual saturation values targeted was different between the two groups. Figure 10 shows the percent of downloaded (actual, unblinded) oxygen saturation values that were recorded at each oxygen saturation level from SpO_2 80% to the maximum SpO_2 100%. The median saturation value for each group was within the desired target range: 93% (IQR 90-96) for the standard group who were to target the SpO_2 91-94% range, and 97% for the higher group who were to target a SpO_2 range of 95-98%.

An early analysis (9 months after recruitment commencement) of these data revealed non-compliance (time spent in target range <40%) was occurring in more than 40% of downloads in 5 participating centres. Several remedial measures were undertaken with the staff of these centres to achieve the final desired level of protocol adherence seen in Figure 10, with only two of the eight recruitment centres having unsatisfactory compliance in the final analysis.

Figure 10: Distribution of actual saturation values targeted
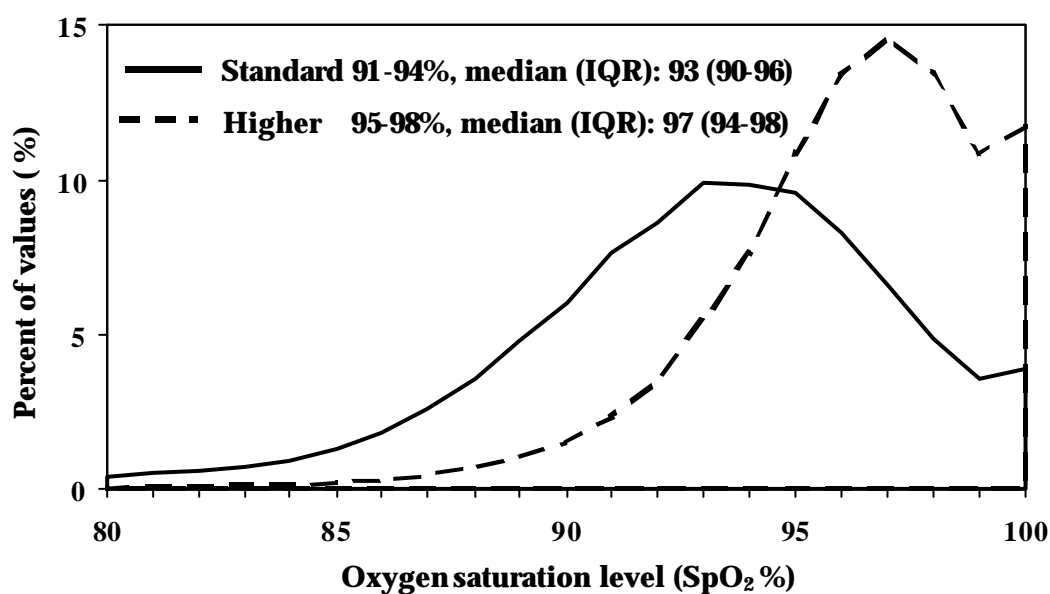
3.3.4 Degree of treatment group crossover

The degree of crossover between the two treatment groups is summarised in Table 5. Thirty seven percent (37%) of median saturation values for infants assigned to the standard group were in the higher range or above, and 25% of median saturation values of infants assigned to the higher group were in the standard range or lower. The median saturation value was in the desired target range for 36% of the time for the standard group and for 52% of the time for the higher group. This was close to the expected time in the target range (over 40%) given the relatively tight target ranges and the pragmatic nature of the trial design. There was no clinically significant difference between the two groups in the proportion of very low saturation values (SpO_2 <85%) with 7% of saturation values recorded at less than this level in the standard group and 2% of values lower than SpO_2 85% in the higher target range group.

Table 5: Percentage distribution of infants according to median pulse oximetry for all downloads in oxygen - degree of "crossover" between treatment groups

Median pulse oximetry value for all downloads in oxygen	Standard target range SpO_2 91-94%* n=134	Higher target range SpO_2 95-98%* n=162
<89	16.4	3.7
89	4.8	1.1
90	6.0	1.5
91	7.6	2.3
92	8.6	3.5
93	9.9	5.5
94	9.8	7.6
95	9.6	10.8
96	8.3	13.3
97	6.6	14.6
98	4.9	13.5
99	3.6	10.9
100	3.9	11.7

The | symbols indicate the targeted ranges of saturation values for each arm of the study.

* Each study arm column gives the percentage of all subjects in that column whose median pulse oximetry whilst in supplemental oxygen was at the level shown in the left hand column.

3.3.5 Proportion of motion artefact

Artefactual saturation readings caused by vigorous movement of the limb to which the saturation probe is attached can be one of the disadvantages of using this technology in non-anaesthetised infants. The type of oximeter used in the trial, the Nellcor N-3000, purports to minimise motion artefact[174] and the levels seen seem to confirm this. Overall, only 3.2% of the readings were affected by motion artefact: 2.1% of readings in the standard group and 3.9% of readings in the higher group. The level of motion artefact is considerably lower than that reported in other studies of neonates[264] which can be as high as 20-30% of the total saturation values.

3.3.6 Permitted protocol violations

Permitted protocol violations for open oxygen saturation targeting (as described in section 2.1.3) occurred relatively infrequently and were equally distributed between the two groups (Table 6). The most common reason for protocol violation was to treat threshold ROP with either high oxygen targeting and/or ablative retinal surgery. A smaller number of infants violated the protocol when high oxygen targeting was ordered following abnormal sleep studies. Parental request or problems with the study oximeter or the downloading programme were relatively uncommon reasons for protocol violation. Of the 26 infants who violated the protocol in the standard range group, 13 did so only temporarily, for a median of 3 days (IQR 1-17), compared with 14/28 infants in the higher range group who had a median of 5 days (IQR 1-8) of temporary protocol violation (Table 7).

Table 6: Reasons for permitted protocol violations - temporary and permanent

Reason	SpO_2 91-94% N=178	SpO_2 95-98% N=180
	Number (%)	
ROP treatment (high O_2, cryotherapy)	9	9
After sleep study (ordered high O_2)	3	6
Hernia surgery	4	1
Clinically unwell e.g. sepsis	6	5
Parental request	3	5
Oximeter or downloading problems	1	2
Total	26 (15%)	28 (16%)

Table 7: Numbers of permitted protocol violations - temporary and permanent

Type of protocol violation	SpO$_2$ 91-94% N=178	SpO$_2$ 95-98% N=180
	Number	
Temporary*	13	14
Permanent	13	14
Total	26	28

The 13 infants in the standard range group who violated the protocol temporarily did so for a median of 3 days (IQR 1-17), compared with 14 infants in the higher range group who had a median of 5 days (IQR 1-8) of temporary protocol violation.

3.4 Primary outcomes

3.4.1 Follow-up rates and missing data

Primary outcome ascertainment rates were 93% in both the standard and higher target range groups (see Figure 7). Of the 334 infants assessed at approximately 12 months corrected age, 96% (n=321) underwent a Revised Griffiths assessment (95% in the standard group and 98% in the higher group). 72% (n=232) of these infants were assessed by one of the nine trained Griffiths assessors located at the eight recruitment centres. A small number of infants (n=13) were unable to be assessed using the Revised Griffiths Scale. Whenever possible the original version of the Griffiths Developmental Scale was used as an alternative (n=9). One infant was assessed using the Bayley Scale[210, 265] and 3 infants had other types of validated developmental assessments. 10 infants still alive at 12 months corrected age (7 in the standard group and 3 in the higher group) did not undergo a formal developmental assessment. The baseline characteristics of infants with missing primary outcome data (due to death, n=14, or lost to follow-up, n=10) did not differ significantly from those with outcome data available at 12 months corrected age (Table 8; see also Table 2).

The median age at primary outcome assessment did not differ between the two groups: 12.1 (IQR 11.8-12.7) and 12.2 (IQR 11.9-12.9) months corrected age in the standard and higher groups, respectively.

Table 8: Baseline infant and parental characteristic for infants with missing primary outcome data

Variable	SpO$_2$ 91-94% Control group N=12	SpO$_2$ 95-98% Treatment group N=12	Both groups N=24
Gestational age	26.0 weeks (SD 1.7)	26.4 weeks (SD 1.8)	26.2 weeks (SD 1.7)
Male gender	6 (50.0%)	7 (58.3%)	13 (54.2%)
Birth weight	869.0 grams (SD 217.3)	908.4 grams (SD 258.1)	888.3 grams (SD 236.4)
Birth head circumference	24.3 cm (SD 2.0)	24.7 cm (SD 2.3)	24.5 cm (SD 2.2)
Birth length	35.1 cm (SD 3.6)	35.4 cm (SD 4.7)	35.2 cm (SD 4.1)
Singletons	10 (83.3%)	8 (66.6%)	18 (75.0%)
5 minute Apgar <7	3 (25.0%)	4 (33.3%)	7 (29.2%)
Born in tertiary hospital with NICU	10 (83.3%)	11 (91.7%)	21 (87.5%)
Surfactant	10 (83.3%)	10 (83.3%)	20 (83.3%)
PDA	6 (50.0%)	6 (50.0%)	12 (50.0%)
Apnoea/bradycardia requiring treatment	10 (83.3%)	9 (75.0%)	19 (79.2%)
Days TPN	15.5 days (IQR 9.5-24.5)	14.0 days (IQR 6-22)	14.0 days (IQR 8-24)
No NEC	10 (83.3%)	11 (91.2%)	21 (87.5%)
Worst IVH Grade 3, 4 or PVL	0 (0%)	1 (8.3%)	1 (4.2%)
Days mechanical ventilation (via ETT)	24.0 days (IQR 5.5-39)	8.0 days (IQR 3-31)	17.0 days (IQR 3-36)
HFV	3 (25.0%)	2 (16.7%)	5 (20.8%)
Antenatal steroids (any)	10 (83.3%)	10 (83.3%)	20 (83.3%)
Maternal tertiary education	4 (33.3%)	2 (16.7%)	6 (25.0%)
Paternal tertiary education	4 (33.3%)	3 (25.0%)	7 (29.2%)
Mother's usual occupation score	4.8 (SD 1.1)	4.1 (SD 2.0)	4.4 (SD 1.6)
Father's usual occupation score	4.8 (SD 1.2)	4.8 (SD 1.9)	4.8 (SD 1.5)
Mother's height	161.1 cm (SD 8.3)	165.6 cm (SD 7.9)	163.4 (SD 8.3)
Father's height	173.6 cm (SD 9.1)	173.3 cm (SD 8.3)	173.4 (SD 8.5)
Mean EPDS at entry	11.4 (SD 5.1)	9.7 (SD 4.7)	10.7 (SD 4.9)
Proportion with EPDS > 12 at entry	3 (25.0%)	2 (16.7%)	5 (20.8%)
Maternal age (years)	28.8 (SD 5.80)	24.9 (SD 5.1)	27.0 (SD 5.8)
Maternal ethnicity Caucasian	8 (66.7%)	8 (66.7%)	16 (66.7%)

3.4.2 Growth outcomes

There were no significant differences between the two groups for any growth measures at any of the follow-up time-points: 38 weeks pma, 4 or 12 months corrected age (Table 9). These included measures of mean weight, length or head circumference. The mean weight of infants at 12 months corrected age was 9.10 kg (SD 1.5) and 9.25 kg (SD 1.6) in the standard and higher groups respectively.

Table 9: Growth outcomes, by treatment group

Variable	SpO$_2$ 91-94% Control group N=178	SpO$_2$ 95-98% Treatment group N=180	Mean Difference or Relative Risk [95% CI]
Mean wt at 38 wks pma	2345g (SD 429, N=175)	2369g (SD 428, N=178)	MD 24g [-66.1, 113.3] P=0.6
Mean leng at 38 wks pma	44.2cm (SD 3.2, N=172)	44.2cm (SD 3.2, N=167)	MD 0.0cm [-0.63, 0.73] P=1.0
Mean hc at 38 wks pma	33.1cm (SD 2.2, N=176)	32.9cm (SD 1.9, N=178)	MD -0.2cm [-0.67, 0.18] P=0.3
Mean wt at 4 mths corr	5845g (SD 1161, N=167)	5811g (SD 1141, N=168)	MD -34.1g [-281.5, 213.3] P=0.8
Mean leng at 4 mths corr	60.1cm (SD 4.4, N=157)	59.3cm (SD 4.7, N=162)	MD -0.8cm [-1.88, 0.13] P=0.1
Mean hc at 4 mths corr	41.3cm (SD 1.8, N=161)	41.2cm (SD 1.8, N=161)	MD -0.1cm [-0.53, 0.27] P=0.5
Mean wt at 12 mths corr	9.10kg (SD 1.5, N=165)	9.25kg (SD 1.6, N=168)	MD 0.15kg [-0.18, 0.49] P=0.4
Mean leng at 12 mths corr	74.0cm (SD 3.9, N=162)	74.1cm (SD 4.1, N=164)	MD 0.1cm [-0.75, 0.98] P=0.8
Mean hc at 12 mths corr	46.3cm (SD 2.0, N=165)	46.3cm (SD 1.9, N=165)	MD 0.0cm [-0.40, 0.44] P=1
Mean wt at 12 mths corr for only infants with wt <3rd centile	7.30 kg (SD 0.6, N=34)	7.18 kg (SD 0.7, N=31)	MD –0.12kg [-0.44, 0.20] P=0.5
wt <10th centile at 12 mth	61 (37.0%, N=165)	55 (32.7%, N=168)	RR 0.89 [0.66, 1.19] P=0.4
leng <10th centile at 12 mth	42 (25.9%, N=162)	41 (25.0%, N=164)	RR 0.96 [0.67, 1.40] P=0.8
Hc <3rd centile at 12 mth	5 (3.0%, N=165)	8 (4.9%, N=165)	RR 1.60 [0.53, 4.79] P=0.4
wt < 3rd centile at 12 mth	34 (20.0%, N=165)	31 (18.5%, N=168)	RR 0.92 [0.59, 1.43] P=0.7

pma = postmenstrual age, wt = weight, leng = length, hc = head circumference, mths corr = months of corrected age, N = number in denominator, SD = standard deviation

Similarly, the proportion of infants small for their age at 12 months corrected age (for either weight, length or head circumference) was not significantly different between the two groups (Table 9). This included the primary outcome of the proportion of infants with weight less than the 10th centile at 12 months corrected age which showed a relative risk of 0.89 (95% CI 0.66 1.19; P=0.4) (see Figure 11). When a more stringent criterion of poor growth, weight less than the 3rd centile at 12 months corrected age, was examined the results remain non-significant (Table 9, and Figure 12). The proportion of infants with weight less than the 3rd centile at 12 months corrected age was 20% in the standard group and 19% in the higher target range group (RR 0.92; 95% CI 0.59,1.43; P=0.7).

Figure 11: Boxplot of main primary outcomes

Outcome	SpO$_2$ 95 -98% n/N	SpO$_2$ 91 -94% n/N	RR 95% CI	RR 95% CI	p value
Wt<10th% 12mth	55/168	61/165		0.89 [0.66, 1.19]	p=0.4
Major dev abn 12mth	39/168	40/166		0.96 [0.66, 1.42]	p=0.8

0.1   02   1   5   10

Favours SpO$_2$ 95-98%   Favours SpO$_2$ 9 -94%
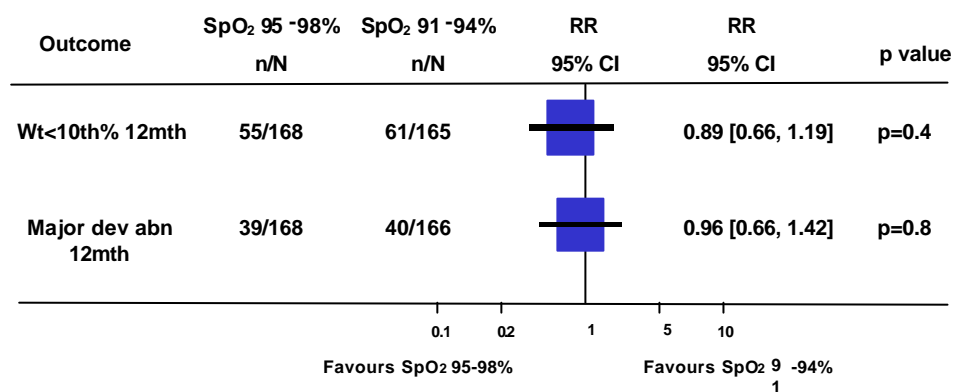
Figure 12: Box and whisker graph of growth in infants with mean weight <3rd centile compared with all infants at 12 months corrected age
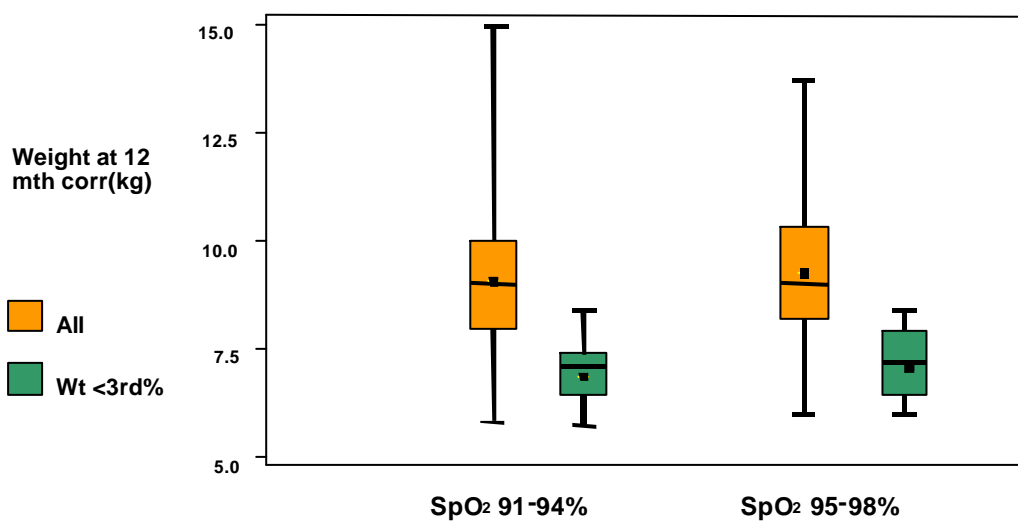
3.4.3 Developmental outcomes

There were no significant differences in any of the developmental measures, assessed at 12 months corrected age (Table 10). This included the primary developmental outcome of the proportion of infants with a major developmental abnormality (RR 0.96; 95% CI 0.66, 1.42; P=0.8) (see also Figure 11). It should be noted that the mean Revised Griffiths Developmental Quotient (DQ) score for both groups (88.3 and 86.8 for the standard and higher groups respectively) was more than one standard deviation below the mean for normal, full term children (-1 SD = 88.7).[206] This low mean developmental score is similar to that found in other populations of preterm infants at one year corrected age.[212, 213, 266] The proportion of infants with a Revised Griffiths Developmental Quotient (DQ) score more than one, but less than two, standard deviations below the mean was also similar in the two groups: 19% and 20% for the standard and higher groups respectively (RR 1.08; 95% CI 0.69, 1.69; P=0.7).

Table 10: Developmental outcomes for all infants, by treatment group

Variable	SpO$_2$ 91-94% Control group	SpO$_2$ 95-98% Treatment group	Relative Risk or Mean Difference [95% CI]
Major dev abnormal at 12 mths corr (CP or blind or DQ <2SD below mean)	40 (24.1%, N=166)	39 (23.2%, N=168)	RR 0.96 [0.66, 1.42] P=0.8
CP rate at 12 mths corr	11 (6.6%, N=166)	16 (9.5%, N=168)	RR 1.44 [0.69, 3.00] P=0.3
Mean Rev Griffiths score at 12 mths corr	88.3 (SD 18.3, N=158)	86.8 (SD 21.8, N=164)	MD -1.5 [-5.9, 2.9] P=0.5
DQ < 2 SD at 12 mths corr	30 (19.2%, N=156)	34 (20.7%, N=164)	RR 1.08 [0.69, 1.67] P=0.7
DQ < 1 SD at 12 mths corr	63 (40.4%%, N=156)	71 (43.3%, N=164)	RR 1.07 [0.83, 1.39] P=0.6
DQ between 1 and 2 SD below mean at 12 mths corr	29 (18.6%, N=156)	33 (20.1%, N=164)	RR 1.08 [0.69, 1.69] P=0.7

dev abn = developmental abnormality, CP = cerebral palsy, DQ = developmental quotient, Rev Griffiths = Revised Griffiths Developmental Scale, mths corr = months of corrected age, SD = standard deviation

3.4.4 <u>Growth and development outcomes for *a priori* sub-groups</u>

When the primary growth outcomes were examined in the sub-group of 256 high risk infants born at less than 28 weeks' gestation, there were no statistically significant differences in any of the growth and developmental outcomes between the two groups (Table 11). Similarly, in the sub-group of 84 infants who were discharged home whilst still receiving supplemental oxygen, all the differences in primary growth and development outcomes remained non-significant (Table 12).

Table 11: Primary outcomes for 256 infants born at less than 28 weeks' gestation

Variable	SpO_2 91-94% Control group N=124	SpO_2 95-98% Treatment group N=132	Mean Difference or Relative Risk [95% CI]
Mean wt at 38 wks pma	2321g (SD 437, N=121)	2369g (SD 409, N=131)	MD 48g [-57.6, 152.4] P=0.4
Mean leng at 38 wks pma	43.9cm (SD 3.2, N=120)	43.9cm (SD 3.0, N=121)	MD 0.0cm [-0.71, 0.86] P=0.8
Mean hc at 38 wks pma	32.9cm (SD 2.2, N=122)	32.7cm (SD 2.0, N=131)	MD -0.2cm [-0.73, 0.30] P=0.4
Mean wt at 12 mths corr	8.91kg (SD 1.4, N=115)	9.13kg (SD 1.5, N=122)	MD 0.23kg [-0.60, 0.15] P=0.2
Mean leng at 12 mths corr	73.8cm (SD 3.9, N=112)	74.0cm (SD 4.1, N=118)	MD 0.2cm [-0.85, 1.23] P=0.7
Mean hc at 12 mths corr	46.0cm (SD 1.7, N=115)	46.0cm (SD 1.9, N=121)	MD 0.0cm [-0.41, 0.52] P=0.8
Wt <10th centile At 12 mth	44 (38.3%, N=115)	39 (32.0%, N=122)	RR 0.84 [0.59, 1.18] P=0.3
Length <10th centile At 12 mth	30 (26.8%, N=112)	29 (24.6%, N=118)	RR 0.92 [0.59, 1.42] P=0.7
HC <3rd centile At 12 mth	5 (4.3%, N=115)	7 (5.8%, N=121)	RR 1.33 [0.43, 4.07] P=0.6
Major dev abn at 12 mth corr (CP or blind or DQ <2SD below mean)	32 (27.8%, N=115)	27 (22.1%, N=122)	RR 0.80 [0.50, 1.20] P=0.3

Table 12: Primary outcomes for 84 home oxygen infants

Variable	SpO$_2$ 91-94% Control group N=30	SpO$_2$ 95-98% Treatment group N=54	Mean Difference or Relative Risk [95% CI]
Mean wt at 38 wks pma	2331g (SD 509)	2353g (SD 468)	MD 22g [-196.7, 240.9] P=0.8
Mean length at 38 wks pma	43.5cm (SD 3.7)	43.7cm (SD 3.2)	MD 0.2cm [-1.46, 1.70] P=0.9
Mean hc at 38 wks pma	32.7cm (SD 2.4)	32.4cm (SD 2.0)	MD -0.3cm [-1.27, 0.70] P=0.5
Mean wt at 12 mths corr	9.21kg (SD 2.1)	9.27kg (SD 1.5)	MD 0.06kg [-0.76, 0.89] P=0.9
Mean length at 12 mths corr	74.0cm (SD 4.8)	74.0cm (SD 4.1)	MD 0cm [-2.1, 2.0] P=1.0
Mean hc at 12 mths corr	46.5cm (SD 3.3)	46.3cm (SD 1.9)	MD -0.2cm [-1.4, 0.94] P=0.7
Wt <10th centile at 12 mth	12 (40%)	14 (26%)	RR 0.65 [0.35, 1.22] P=0.2
Length <10th centile at 12 mth	9 (30%)	14 (26%)	RR 0.86 [0.43, 1.76] P=0.7
HC <3rd centile at 12 mth	1 (3.3%)	3 (5.6%)	RR 1.67 [0.18, 15.33] P=0.7
Major dev abn at 12 mth corr (CP or blind or DQ <2SD below mean)	13 (45%, N=29)	17 (33%, N=51)	RR 0.74 [0.42, 1.30] P=0.3

3.5 Secondary outcomes

3.5.1 Oxygen therapy outcomes

The proportion of infants still oxygen dependent at 36 weeks pma was significantly higher for those targeting the higher saturation range (64%) compared with infants in the standard range group (46%) (RR 1.40, 95% CI 1.15, 1.70; P=0.0006) (Table 13, Figure 13). An event rate difference of this magnitude results in a number needed to harm[267] of 6 (1/(0.644 - 0.461) = 5.46, 95% CI 3,14). That is, for every 6 infants targeted at the higher saturation range, one additional case of oxygen dependency at 36 weeks pma could be expected.

Table 13: Oxygen therapy outcomes for all infants, by treatment group

Variable	SpO$_2$ 91-94% Control group N=178	SpO$_2$ 95-98% Treatment group N=180	Relative Risk or Median Difference [95% CI]
Supplemental oxygen at 36 wks pma	82 (46.1%)	116 (64.4%)	RR 1.40 [1.15, 1.70] P=0.0006
Total days of oxygen	56 days (IQR 38-89)	72 days (IQR 53-123)	MedD 19 [10, 27] P<0.0001
Days oxygen after randomisation	18 days (IQR 7-41)	40 days (IQR 21-73)	MedD 17 [12, 23] P<0.0001
pma when oxygen ceased	35.4 wks (IQR 33-40)	37.9 wks (IQR 35-45)	MedD 2.3 [1.3, 3.3] P<0.0001
Home oxygen	30 (16.9%)	54 (30%)	RR 1.78 [1.20, 2.64] P=0.004
Days of home oxygen	92 (IQR 34-208, N=30)	99 (IQR 53-199, N=54)	MedD 11 [-28, 57] P=0.5

Figure 13: Boxplot of significant secondary outcomes

Outcome	SpO$_2$ 95-98% n/N	SpO$_2$ 91-94% n/N	RR 95% CI	RR 95% CI	p value
O$_2$ 36 wks pma	116/180	82/178		1.40 [1.15 1.70]	p=0.0006
Home oxygen	54/180	30/178		1.78 [1.20, 2.64]	p=0.004

0.1　0.2　1　5　10

Favours SpO$_2$ 95-98%　　　　Favours SpO$_2$ 91-94%
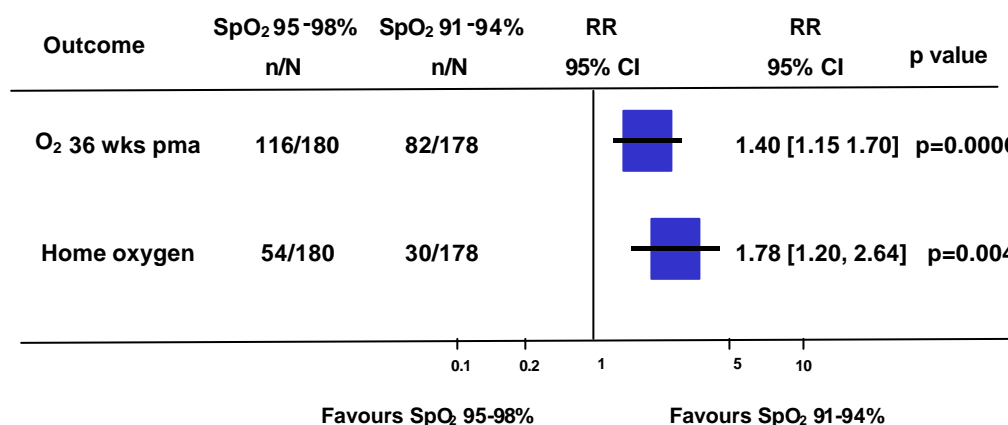
Measures of oxygen supplementation duration were significantly longer in the higher target range group (Table 13). The total days of oxygen supplementation was a median of 56 days (IQR 38-89) in the standard group compared with a median of 72 days (IQR 53-123) in the higher group (MedD 19 days; 95% CI 10, 27; P<0.0001). Similarly, the days of oxygen supplementation after randomisation was significantly different between the two groups: 18 days (IQR 7-41) in the standard group versus 40 days (IQR 21-73) in the higher target group (MedD 17 days; 95% CI 12, 23; P<0.0001). The postmenstrual age when oxygen was ceased was also significantly different at 35.4 weeks (IQR 33-40) in the standard group compared with 37.9 weeks (IQR 35-45) in the higher group (MedD 2.3 weeks; 95% CI 1.3, 3.3; P<0.0001).

This increased duration of oxygen therapy in the higher target range group resulted in significantly more infants being discharged home on supplemental oxygen (Table 13 and Figure 13). The proportion of infants receiving home oxygen was significantly higher in the higher range group (30%) compared with the standard target range group (17%) (RR 1.78, 95% CI 1.20, 2.64; P=0.004). If translated into a number needed to harm (NNH), this would mean that for every 8 infants treated with higher oxygen targeting one additional case of home oxygen could be expected (1/(0.300 - 0.169) = 7.6, 95% CI 4, 29). Although significantly more infants received supplemental oxygen after discharge, the duration of home oxygen was not different between the two groups. Infants in the standard range group who went home on oxygen received this therapy for a median of 92 days (IQR 34-208) after discharge, whilst those in the higher target range group had a median duration of home oxygen of 99 days (IQR 53-99) (MedD 11 days; 95% CI -28, 57; P=0.5).

3.5.2 Clinical outcomes

None of the other clinical outcomes collected during the infants' initial hospitalisation were significantly different between the two groups (Table 14). This included the use of postnatal corticosteroids or diuretics for chronic lung disease, the length of hospital stay (either in total or after randomisation), pma at discharge, pma to reach full sucking feeds, total days of assisted ventilation, or days of assisted ventilation after randomisation (for those infants who ceased assisted ventilation after randomisation).

Table 14: Clinical outcomes for all infants, by treatment group

Variable	SpO$_2$ 91-94% Control group N=178	SpO$_2$ 95-98% Treatment group N=180	Relative Risk or Median Difference [95% CI]
Postnatal steroids	89 (50%)	104 (57.8%)	RR 1.16 [0.95, 1.40] P=0.14
Diuretics for CLD	78 (43.8%)	93 (51.7%)	RR 1.18 [0.95, 1.47] P=0.14
Length of hospital stay (days)	85.0 (IQR 74-107)	92.0 (IQR 77-106.5)	MedD 4 [-1, 9] P=0.9
Length of stay, after randomisation (days)	50.0 (IQR 39-60)	50.0 (IQR 42-61.5)	MedD 2 [-1, 5] P=0.2
pma at discharge (weeks)	39.1 (IQR 37-40)	39.1 (IQR 38-41)	Med D 0.3 [-0.1, 0.9] P=0.2
pma at full sucking feeds (weeks)	37.7 (IQR 37-39)	37.7 (IQR 36-39)	MedD -0.4 [-0.9, 0] P=0.9
Days assisted ventilation (all types)	31.0 (IQR 17-54)	37.0 (IQR 19-52)	MedD -5 [-10, 0] P=0.3
Days assisted ventilation (all types), after randomisation - only if ended ventilation after randomisation	14.0 (IQR 7-28)	14.0 (IQR 6-35)	MedD 0 [-4, 4] P=0.9
Death (all causes) by 12 mths corr	5 (2.8%)	9 (5.0%)	RR 1.78 [0.61, 5.21] P=0.3
Death (pulmonary causes) by 12 mths corr	1 (0.6%)	6 (3.3%)	RR 5.93 [0.72, 48.79] P=0.1

3.5.3 Deaths

There was no significant difference in the numbers of deaths, from randomisation to 12 months corrected age, between the standard (n=5, 2.8%) and higher (n=9, 5.0%) target range groups (RR 1.78, 95% CI 0.61, 5.21; P=0.3). Of these deaths, one was due to pulmonary causes in the standard oxygen target group, compared with 6 in the higher range group (RR 5.93 95% CI 0.72, 48.79; P=0.1) (Table 14). One death in the standard range group occurred after discharge from the infant's initial hospitalisation compared with 5 post-discharge deaths in the higher target group (Table 15).

Table 15: Causes and timing of post-randomisation deaths, by treatment group

Treatment Allocated	Cause of death	pma at discharge (weeks)	pma at death (weeks)
SpO$_2$ 91-94% Control group			
	Hypertrophic obstructive cardiomyopathy	38	38
	Intestine, acute vascular insufficiency	34	34
	NEC	33	33
	Pneumonia	39	39
	SIDS	42	**61**
SpO$_2$ 95-98% Treatment group			
	Abdominal abscess, treatment withdrawn	36	36
	NEC	32	32
	Respiratory failure	48	48
	Respiratory failure	39	39
	Respiratory failure	37	**92**
	Chronic lung disease	49	**60**
	Chronic lung disease	41	**73**
	Pneumonia	41	**43**
	SIDS	39	**46**

3.5.4 Ophthalmic outcomes

There were no statistically significant differences in the rates of any stage of retinopathy of prematurity, nor in the need for ablative retinal surgery (20/178, 11%, in the standard group versus 11/180, 6%, in the higher group, P=0.09) (Table 16).

Table 16: Ophthalmic outcomes, by treatment group

Variable	SpO$_2$ 91-94% Control group	SpO$_2$ 95-98% Treatment group	Relative Risk [95% CI]
All infants:			
Worst ROP = none	97 (54.5%, N=178)	94 (52.2%, N=180)	RR 0.96 [0.79, 1.16] P=0.7
Worst ROP = stage 1	12 (6.7% N=178)	14 (7.8%, N=180)	RR 1.15 [0.55, 2.42] P=0.7
Worst ROP = stage 2	41 (23.0%, N=178)	50 (27.8%, N=180)	RR 1.21 [0.84, 1.72] P=0.3
Worst ROP = stage 3	27 (15.2%, N=178)	22 (12.2%, N=180)	RR 0.8 [0.48, 1.36] P=0.4
Worst ROP = stage 4	1 (0.6%, N=178)	0 (0%, N=180)	RR 0.33 [0.01, 8.04] P=0.5
Worst ROP = stage 3 or 4	28 (15.7%, N=178)	22 (12.2%, N=180)	RR 0.78 [0.46, 1.30] P=0.3
Retinal ablative surgery	20 (11.2%, N=178)	11 (6.1%, N=180)	RR 0.54 [0.27, 1.10] P=0.09
Blind at 12 mths corr (unilateral or bilateral)	4 (2.4%, N=166)	1 (0.6%, N=168)	RR 0.25 [0.03, 2.19] P=0.2
Poor eye outcome by 12 months corr (ROP stage 3/4 or ablative retinal surgery or blind)	31 (17.7%, N=175)	22 (12.4%, N=178)	RR 0.70 [0.42, 1.16] P=0.2
Infants <28 weeks' gestation only:			
Worst ROP = stage 3 or 4	28 (22.6%, N=124)	21 (15.9%, N=132)	RR 0.70 [0.42, 1.17] P=0.18
Retinal ablative surgery	20 (16.1%, N=124)	11 (8.3%, N=132)	RR 0.52 [0.26, 1.03] P=0.06
Blind at 12 mths corr (unilateral or bilateral)	4 (3.4%, N=118)	1 (0.8%, N=122)	RR 0.24 [0.03, 2.13] P=0.2
Poor eye outcome by 12 months corr (ROP stage 3/4 or ablative retinal surgery or blind)	31 (17.7%, N=122)	21 (12.4%, N=131)	RR 0.63 [0.38, 1.04] P=0.07

All but one infant with severe ophthalmic outcomes (worst stage ROP = 3 or 4, ablative retinal surgery or blindness, N=52) was less than 28 weeks' gestation at birth, and all but one of these infants retained vision in at least one eye (1 case bilateral blindness in standard target range group). All infants who required ablative retinal surgery (N=31) were less than 28 weeks' gestation at birth. The rates of ablative retinal surgery in this sub-group of infants were 16% (20/124) in the standard target range group, compared with 8% (11/132) in the higher target range group (RR 0.52, 95% CI 0.26, 1.03; P=0.06) (Table 16).

3.5.5 Psychosocial outcomes

The follow-up rates for the self-administered questionnaires assessing the psychosocial outcomes ranged from 71-77%. There were no significant differences between the groups in the measures of postnatal depression, infant or toddler temperament, parenting stress, or family impact (Table 17). Edinburgh Postnatal Depression Scale (EPDS) scores decreased over time from a mean of 10.4 (SD 5.5) at enrolment to 6.2 (SD 4.9) when assessed at 12 months corrected age. The proportion of mothers with an elevated EPDS score (>12)[191] was 32% (88/272), 18% (45/252), 8% (20/248) and 11% (30/265) at 32 weeks pma, 38 weeks pma, 4 and 12 months corrected age respectively. The high rates of elevated EPDS during the infant's initial hospitalisation are similar to those reported in other extremely preterm populations.[225]

Table 17: Psychosocial outcomes, by treatment group

Variable	SpO$_2$ 91-94% Control group	SpO$_2$ 95-98% Treatment group	Mean Difference [95% CI]
Mean EPDS at 32 weeks pma	10.7 (SD 5.7, N=138)	10.0 (SD 5.3, N=134)	MD -0.7 [-2.03, 0.60] P=0.4
Mean EPDS at 38 weeks pma	7.5 (SD 5.0, N=124)	8.1 (SD 5.5, N=128)	MD 0.6 [-0.78, 1.9] P=0.4
Mean EPDS at 4 mths corr	5.6 (SD 4.5, N=123)	6.5 (SD 5.3, N=125)	MD 0.9 [-0.38, 2.1] P=0.2
Mean EPDS at 12 mths corr	5.9 (SD 5.1, N=135)	6.5 (SD 4.8, N=130)	MD 0.6 [-0.6, 1.8] P=0.3
Mean ITS at 4 mths corr	2.3 (SD 0.7, N=126)	2.4 (SD 0.7, N=129)	MD 0.1 [0.0, 0.3] P=0.06
Mean TTS at 12 mths corr	3.2 (SD 0.6, N=132)	3.1 (SD 0.6, N=133)	MD -0.1 [-0.2, 0.1] P=0.6
Mean PSI at 12 mths corr	71.7 (SD 20.6, N=132)	72.9 (SD 21.1, N=129)	MD 1.2 [-3.9, 6.3] P=0.7
Mean IFS at 12 mths corr	40.0 (SD 11.0, N=131)	39.8 (SD 11.7, N=127)	MD -0.20 [-2.98, 2.59] P=0.9

3.5.5.1 Psychosocial outcomes for home oxygen sub-group

Psychosocial outcomes were examined for the sub-group of infants who received home oxygen therapy (N=84) as families of these infants are known to have increased psychological stress.[268] Data from this trial showed that infants receiving home oxygen were rated as having a more difficult temperament at 4 months corrected age than those infants not receiving home oxygen (mean difference in infant temperament scores 0.2; 95% CI 0.06, 0.46; P=0.01), and their parents had higher parenting stress index scores (70.8 for the no home oxygen group versus 67.5 for the home oxygen group; MD 5.7; 95% CI -0.02, 11.42; P=0.05). However, it should be noted that these sub-group analyses were not done on the groups as originally randomised and thus these results should be treated with caution.

3.5.6 Health service utilisation and rehospitalisation outcomes

Measures of health service utilisation and rehospitalisation rates in the first year of life did not differ by treatment group (Table 18). The proportion of infants visited by a family support team[269, 270] was 44% (158/358). The median number of health service usages in the first year of life was 27.5 visits per infant (IQR 25-30) for the standard range group and 31.3 visits per infant (IQR 27-35) for the higher range group (MedD 3.8; 95% CI -0.84, 8.51; P=0.1). Rehospitalisation was quite common for trial infants in the first year with 51% (174/341) being readmitted at least once. However only a small proportion of these readmissions (5.5%, 25 of 452 readmissions) were for an illness severe enough to require the infant to be re-ventilated or receive intensive care.

Table 18: Health service utilisation and rehospitalisation outcomes, by treatment group

Variable	SpO$_2$ 91-94% Control group	SpO$_2$ 95-98% Treatment group	Relative Risk or Median Difference [95% CI]
Family support team visited	78 (43.8%, N=178)	80 (44.4%, N=180)	RR 1.01 [0.08, 1.28] P=0.9
Median health service usages to 12 mths corr	27.5 visits/infant (IQR 25-30, N=171)	31.3 visits/infant (IQR 27-35, N=170)	MedD 3.8 [-0.84, 8.51] P=0.1
# infants rehospitalised to 12 mths corr	82 (48%, N=171, 212 readmissions)	92 (54%, N=170, 240 readmissions)	RR 1.13 [0.92, 1.39] P=0.3
# readmissions requiring mechanical ventilation	7 (3.3%, N=212 readmissions)	11 (4.6%, N=240 readmissions)	RR 1.39 [0.55, 3.52] P=0.5
# readmissions to ICU	10 (4.7%, N=212 readmissions)	15 (6.2%, N=240 readmissions)	RR 1.32 [0.61, 2.89] P=0.5

3.5.6.1 <u>Health service utilisation and rehospitalisation outcomes for home oxygen sub-group</u>

Health service utilisation and rehospitalisation outcomes were examined more comprehensively for the sub-group of infants who received home oxygen therapy as these infants are known to have increased health service needs.[22, 113, 271-273] These outcomes in the home oxygen infants (N=84) compared with trial infants who did not receive home oxygen (N=274) are summarised in Table 19. This analysis revealed infants receiving home oxygen are significantly more likely to be visited by a family support team (RR 1.55; 95% CI 1.24, 1.95, P=0.0001) and have an increased number of health service usages, with 31 visits per infant for the home oxygen group compared with 24.5 visits per infant for those not receiving home oxygen (MedD -8; 95% CI -12, -3; P=0.001). A greater proportion of home oxygen infants also required rehospitalisation with 65% of home oxygen infants compared with 47% of non-home oxygen infants being readmitted in the first year of life (RR 1.40; 95% CI 1.14, 1.72; P=0.001). They also had a significantly increased median number of readmissions (P=0.0001).

3.6 <u>Adjustment of outcomes for known prognostic factors</u>

It was hypothesised that although baseline prognostic characteristics were well balanced between the two groups (see Table 2), adjustment for factors known to strongly predict some of the outcomes in this cohort of infants (gestation, gender, ethnicity, plurality)[28] and the baseline EPDS (which showed a different rate of change over time between the groups, see Table 17) might influence the results. Several clinical outcomes (length of hospital stay or days of mechanical ventilation after randomisation, pma to full sucking feeds, pma at discharge home and worst stage of ROP) as well as longer term growth and development outcomes that were expected to show differences between the two oxygen target range groups did not do so in the unadjusted analysis. Hence adjusted analyses for the aforementioned factors were undertaken using multiple or logistic regression models. None of these outcomes changed from a non-significant to a statistically significant result in the adjusted analyses for either the whole cohort of trial infants or for the sub-group of high risk infants born at less than 28 weeks' gestation (see Tables 20 and 21, Appendix 21).

Table 19: Health service utilisation and rehospitalisation outcomes, by home oxygen status

Variable	No home oxygen N=274	Home oxygen N=84	Relative Risk or Median Difference [95% CI]
Family support team visited	107 (39.1%, N=274)	51 (60.7%, N=84)	RR 1.55 [1.24, 1.95] P=0.0001
median # health services usages	24.5 visits/infant (IQR 16-36)	31 visits/infant (IQR 19-48.5)	MedD -8 [-12, -3] P=0.001
median # emergency room visits/infant	2 (IQR 1-3, n=104 visits)	1.5 (1-3, n=44 visits)	MedD 0 (0, 0) P=0.6
median # GP visits/infant	5 (IQR 2-8, n=231 visits)	4 (IQR 3-8, n=75 visits)	MedD 0 (0, 0) P=0.5
median # ECC visits/infant	5 (IQR 2-10, n=195 visits)	4 (IQR 2-7, n=49 visits)	MedD 1 (-1, 2) P=0.3
median # specialist visits/infant	3 (IQR 2-6, n=194 visits)	6 (IQR 3-8, n=67 visits)	MedD -2 (-3, 1) P<0.0001
# infants rehospitalised	120 (283 readmits, N=258, 47%)	54 (169 readmits, N=83, 65%)	RR 1.40 [1.14, 1.72] P=0.001
median # readmissions/infant	0 (IQR 0-1, Range 0-17)	1 (IQR 0-2.5, Range 0-12)	MedD 0 (0, 0) P=0.0001
# readmissions requiring mechanical ventilation	10 (3.5%, n=283 readmits)	8 (4.7%, n=169 readmits)	RR 1.34 [0.54, 3.33] P=0.5
# readmissions to ICU	13 (4.6%, n=283 readmits)	12 (7.1%, n=169 readmits)	RR 1.55 [0.72, 3.31] P=0.3
# infants needing ICU or mechnical ventilation during readmission	13 (5.0%, N=258 pts)	9 (10.8%, N=83 pts)	RR 2.15 [0.95, 4.85] P=0.06
# readmissions for respiratory illness	175 (62%, n=283 readmits)	109 (65%, n=168 readmits)	RR 1.05 [0.91, 1.21] P=0.5
# readmissions for neurological problems	6 (2.1%, n=283 readmits)	1 (0.6%, n=168 readmits)	RR 0.28 [0.03, 2.31] P=0.2
median LOS per readmission (days)	3 (IQR 1-6, Range 1-366)	2 (IQR 1-5, Range 1-311)	MedD 0 (0, 0) P=0.3
total days rehospitalisation	1690 (N=120 infants, n=283 readmits)	1840 (N=54 infants, n=169 re admits)	P<0.0001

3.7 <u>Major outcomes, stratified by centre</u>

In multicentre trials, centre-adjusted analysis may be useful secondary analyses but should not replace the overall results.[254] Hence, the major outcomes (proportion of infants with weight less than 10th centile at 12 months corrected age, presence of a major developmental abnormality, continuing oxygen requirement at 36 weeks pma, and home oxygen therapy) were examined for each enrolment centre, combined using meta-analysis with a fixed effects model and tested for statistical heterogeneity. The results (see Appendix 22) showed there was homogeneity across centre strata for all four major outcomes, and the combined Mantel-Haenszel test statistics were unchanged from the unadjusted analyses (see Tables 9,10, 13).

3.8 <u>Sensitivity analysis of major outcomes for effect of sibling pairs</u>

There were 25 sibling pairs, termed "related multiples", totaling 50 infants enrolled (see section 2.2.2 and Table 4). They made up 14% (50/358) of the total enrolment cohort. A sensitivity analysis was performed by randomly removing 50% of the related multiples from the dataset and re-analysing the four major outcomes (see Appendix 23). This analysis confirmed that the inclusion of sibling pairs made no difference to the overall results for these major outcomes, confirming that it was unnecessary to adjust the results for correlations between sibling outcomes.

CHAPTER 4: DISCUSSION

4.1 Summary of main results

Targeting a higher oxygen saturation range in chronically oxygen dependent, extremely preterm infants conferred no significant long-term growth or development benefits but did result in some increased health service burdens for these infants. Higher oxygen targeting resulted in 40% more infants being in oxygen at 36 weeks postmenstrual age and 78% more being discharged home on supplemental oxygen. Hence, one could expect an additional case of home oxygen therapy for every 8 infants if higher oxygen saturation ranges were targeted routinely. Thus the routine use of higher oxygen targeting for chronically oxygen-dependent, preterm infants cannot be recommended. The results of this trial should not be extrapolated to practice recommendations for oxygen-dependent, preterm infants prior to 32 weeks postmenstrual age.

4.2 Primary growth and development outcomes

The results of this trial contradict much of the previous physiological, observational and anecdotal evidence regarding the beneficial growth and development effects of higher oxygen targeting in chronically oxygen-dependent, preterm infants (see sections 1.6.3 and 1.6.4). There may be several reasons for this. First, it is well recognised that studies which do not use randomisation in an attempt to overcome potential confounding factors can substantially overestimate the effects of interventions.[274-276] To date, there have been no randomised trials that have assessed the effect of higher oxygen targeting on long-term infant growth and development.[24,87] Hence, the apparent beneficial effects of higher oxygen saturation targeting seen in previous non-randomised studies may have been due to other factors that could not be accounted for in non-randomised trial study designs, such as socioeconomic differences, and differences in clinical practices in different time periods and between different clinicians.

Previous work had addressed only short-term growth and development outcomes, such as growth during initial hospitalisation and intracranial pathology prior to discharge. These

measures are only surrogates for more important, longer term outcomes relating to growth and development. Surrogate outcomes are not always good predictors of the true outcomes of interest even when the correlation between the surrogate and the longer term outcome appears strong.[277-279] Hence, prior work which relied on only short-term surrogate outcomes may have found results that differ from those in this study.

A potential limitation of the study design is that more subtle, longer-term outcomes, such as minor disability, are unable to be detected as early as the 12 months corrected age endpoint used in this trial. However, a Griffiths Developmental Scale score of more than 1 but less than 2 standard deviations below the mean has been shown to be predictive of later minor developmental disability.[211, 280] In our cohort of infants there was no significant difference between the two groups for this outcome (19% and 20% for the standard and higher groups, respectively; RR 1.08, 95% CI 0.69, 1.69; P=0.7), suggesting that the experimental treatment does not affect development in this way and that further longer term follow-up of these children is not justified.

Much of the previous work also selected a particularly high-risk group of infants (preterm infants still oxygen-dependent at 36 weeks pma) on whom the experimental treatment may have been more effective. Our trial enrolled infants with less severe lung disease by choosing an earlier entry point for reasons previously outlined in section 2.1.1. This more pragmatic approach should ensure that the trial's results are more generalisable, but may have contributed to an attenuation of the effect of the treatment.

The trial was not designed to answer the question of how best to monitor preterm infants' oxygen levels during acute respiratory failure in the first weeks of life. This would best be answered in the context of another, well-designed randomised trial and a planning group (including the author) has been formed to achieve this goal.[281] However, a potential limitation of the current study design is that infants were enrolled 3-10 weeks after birth during which time the effect of higher oxygen targeting may have been diluted by targeting practices prior to randomisation. The current study design attempted to overcome the potential, well-recognised effects of differing oxygen targeting policies for titrating and weaning oxygen on

the outcomes by stratifying treatment allocation by enrolment hospital in order to assure a balance of the two treatments within each institution (see section 2.2.2 and Table 4).

The trial had approximately 80% power to detect the differences in effect sizes on which the sample size calculations were made. Although effect size differences of this magnitude (see section 2.7.1.2) may have been optimistic, it was thought that without this size of difference in the primary endpoints clinicians would have remained reluctant to change their practice in response to the trial's results. The 24% rate of major developmental abnormality in the control group of this trial was exactly as estimated for the sample size calculations. The proportion of infants small for their age at 12 months corrected age, the other primary outcome on which the sample size estimations were based, was only 37% in the trial's control group, rather than the estimated 47%. However, the 95% confidence interval seen for this outcome (RR 0.96; 95% CI 0.66, 1.42) suggests sufficient power to detect real differences despite the reduced control event rate. *Post hoc* power calculations showed that the trial's sample size had 79% power to detect a real difference in this outcome.

The study design allowed for the allocation of eligible infants of multiple births to the same treatment group as their siblings (see section 2.2.2). There were 25 such infants in addition to the 333 infants individually randomised (see Figure 7). We believed that very few outcomes (potentially only length of hospital stay) would be substantially influenced by the lack of independence in these sibling pairs. This, coupled with the fact that they only comprised a relatively small proportion of the total sample size (50/358 = 14%), suggested there was no need to adjust the analyses for any correlation of outcomes between siblings. Hence, data from all 358 infants (including the additional 25 related multiple siblings) were included as data from independent individuals in the analyses. The sensitivity analysis undertaken by randomly removing half of the related siblings from the analysis confirmed that their presence made no difference to the overall results for the major outcomes (see Appendix 23).

A final potential limitation of the study was the degree of "crossover" between the two groups with regard to the interventions received. Unlike the only other randomised trial to allocate preterm infants to target a standard or higher oxygen saturation range (but in order to assess

different outcomes), the STOP-ROP trial,[106] whose trial management procedures expended considerable effort to maximise the time infants were in their targeted saturation ranges, BOOST was a pragmatic trial. It was designed to test the effect of employing the two different target saturation range *policies* in the "real world" in order to assess whether the experimental treatment would benefit infants across a range of neonatal care settings. Hence, whilst the research nurses regularly downloaded information regarding protocol adherence and discussed these results with the infants' carers (see sections 2.5.2 and 3.3.4), it was expected that there would be some degree of overlap between the two groups. In the STOP-ROP trial only 8% of saturations for infants targeting the standard group were in the higher range or above, and 2% of saturations for infants assigned to the higher group were in the standard range or lower. In our trial, the corresponding results were 37% and 25%, respectively, with the actual median values of 93% (for the SpO_2 91-94% target group) and 97% (for the SpO_2 95-98%) group (see section 3.3.3). These results suggest that the two groups did in fact receive two different treatments and that the lack of difference between the two groups in terms of primary outcomes was not due to overwhelming crossover of the two treatments. Although there are methods available to attenuate the results of a trial to account for the degree of crossover (whilst still maintaining an intention-to-treat analysis),[282] they were not employed in the analysis as the degree of crossover was thought to be acceptable in the context of the pragmatic trial design. Compliance adjusted analyses were also not considered appropriate for a pragmatic trial design. Such analyses would have been difficult to undertaken as infants were back-transferred to one of 52 non-tertiary hospitals and compliance data obtained from these hospitals could thus not be attributed to the original enrolling hospital. It would be outside the scope of the project's original aim to assess the effect of non-compliance in this way, and such analysis would not assist clinicians trying to choose between the two oxygen saturation range *policies* under study in real clinical practice settings.

4.3 Oxygen outcomes

All measures of oxygen duration were significantly increased in the higher target range group, including the duration of oxygen (in total and after randomisation), postmenstrual age when oxygen therapy was ceased, and the proportion of infants still requiring supplemental oxygen at 36 weeks pma (see section 3.5.1). These results may seem self evident, given that infants in

the higher target range group were required to achieve a higher target oxygen level and would thus be expected to take longer to achieve this milestone. However, this suggests that our original hypothesis (see sections 1.7 and 1.9) that higher oxygen targeting might enhance respiratory health and thus infants in this group may have had decreased duration of oxygen, cannot be supported by data from this trial.

Increases in the duration of oxygen of the magnitude found in this trial would have significant health service implications. There was a median difference in the numbers of days in oxygen after 32 weeks pma of 17 days and a median difference in the postmenstrual age at supplemental oxygen cessation of 2.3 weeks (see Table 13). Higher oxygen targeting resulted in 40% more infants being in oxygen at 36 weeks postmenstrual age (RR 1.4, 95% CI 1.2, 1.7; P=0.0006). These findings have both statistical and clinical significance. Infants requiring supplemental oxygen therapy have a higher level of nursing dependency than those who do not require such therapy.[283] A change in the number of infants with increased nursing dependency of this magnitude could have serious health service implications. Interestingly, although there were significantly more infants requiring supplemental oxygen at 36 weeks pma their respiratory health did not appear worsened by higher oxygen targeting. Infants in the higher target range group did not have an increase in postnatal steroid or diuretic use, or have an increased duration of assisted ventilation as would be expected if their respiratory status was worse than those in the standard group. The length of hospital stay, either in total or after randomisation, was also not different between the two groups (see section 3.5.2), again suggesting that infants targeting the higher oxygen saturation range were not necessarily "sicker" than those targeting the standard range.

These results contrast with the only other randomised trial that has allocated infants to higher versus standard oxygen saturation ranges. The STOP-ROP trial[106] randomised preterm infants with pre-threshold ROP (mean age at randomisation 35.6 weeks) to target higher versus standard oxygen saturation ranges for a minimum of two weeks to assess the effect on progression to threshold ROP. That trial assessed pulmonary measures as secondary outcomes at 3 months corrected age. Whilst the STOP-ROP infants who targeted a higher oxygen saturation range were significantly more likely to be in oxygen at 3 months corrected age

(47% vs 37%, P=0.02), they were also significantly more likely to have at least one marker of poor pulmonary health defined as remaining in hospital, or on oxygen, steroids, methylxanthines or diuretics at 3 months corrected age (57% in the higher group versus 46% in the standard group, P=0.005). Similarly, a recent UK cohort study[91] found that infants targeting a higher saturation range required assisted ventilation and supplemental oxygen for significantly longer than those targeted at lower ranges (31 days of ventilation and 96 days of supplemental oxygen for the higher oxygen target infants versus 14 days of ventilation and 40 days of supplemental oxygen for the standard target range infants, P<0.01). So whilst infants in the BOOST trial did not appear to have signs of increased respiratory ill health and did not require increased length of hospitalisation, the increased duration of oxygen translated into 78% more infants receiving home oxygen therapy (RR 1.78; 95% CI 1.20, 2.64; P=0.004) (see section 3.5.1). Hence one could expect an additional case of home oxygen therapy for every 8 infants if higher oxygen saturation ranges were targeted routinely. Taking an infant home who requires continuous supplemental oxygen is known to cause considerable psychological and physical disruption as well as financial stress for the affected families.[268, 284] Thus, a policy of routine higher oxygen targeting could have major health service implications with little evidence of the growth and development benefits it is hypothesised to achieve.

The economic implications of implementing a policy of routine higher oxygen targeting with regard to home oxygen costs can be summarised as follows. Based on detailed costings done in 1993,[285] the daily cost in 2002 of home oxygen is approximately AUD$144 (converting to 2002 AUD$ rates, source: Reserve Bank of Australia <www.rba.gov.au>). Using the trial results of a 30% home oxygen rate in the higher group compared with a rate of 17% in the standard group (see Table 13), one could expect an additional 131 infants per year to require home oxygen therapy for every 1,000 infants routinely targeted at higher oxygen saturation levels. Assuming the mean days of home oxygen for these additional infants would be 165 (mean days of home oxygen in higher target range group was 165), this would mean an additional AUD$3,112,560 (131 infants x 165 days x $144/day) of unnecessary health care expenditure for every 1,000 infants treated with higher oxygen targeting.

The psychological impact of increased home oxygen rates is more difficult to assess. A *post hoc* sub-group analysis of data from this trial showed that infants who received home oxygen were rated as having a more difficult temperament at 4 months corrected age than those who had not received home oxygen and their parents had higher parenting stress index scores (see section 3.5.5.1). However, it should be noted that as these sub-group analyses were not done on the groups as originally randomised, these results should be treated with caution. There are no randomised controlled trials that have directly addressed the question of whether infants requiring home oxygen (by whatever discharge criteria) grow and develop better if their oxygen saturation levels are targeted at a higher level after discharge, and whether such an intervention has any effects on other important secondary outcomes such as duration of home oxygen, infant temperament, parenting stress or family impact (see section 5.2).

4.4 Pulmonary deaths

The unexpected finding of an excess of pulmonary deaths in infants in the higher target range group (see section 3.5.3) was not statistically significant, but the trial had low power to detect real differences in this outcome as the number of late deaths was very small. Our results are consistent with the findings of the only other trial to randomise preterm infants to differing oxygen saturation target ranges, the STOP-ROP trial.[106] That trial found increased adverse pulmonary sequelae (although not increased pulmonary deaths) in preterm infants with pre-threshold ROP when a higher oxygen saturation range was targeted (see section 4.3). In the BOOST trial there were four deaths after discharge due to respiratory causes in the higher oxygen group compared with no post-discharge respiratory deaths in the standard group (see Table 15, section 3.5.3).

The unexpected finding of increased pulmonary deaths is biologically plausible. There is evidence that the by-products of oxygen metabolism can be toxic, particularly when humans are exposed to high oxygen concentrations in inspired air.[25] It is well demonstrated in animal models that exposure to pure oxygen for only a few hours results in pulmonary capillary endothelial thinning and after 2-5 days of high oxygen exposure alveolar oedema and haemorrhage, hyaline membrane formation and complete destruction of the lung capillary endothelium can be observed.[286] Moreover, it is hypothesised that preterm infants are

particularly susceptible to oxygen-radical injury because of their low levels of anti-oxidants.[287, 288] Oxidative stress increases lung antioxidants in some experimental models of chronic lung disease and hyperoxia is known to affect fetal lung growth. Surfactant production and function are also altered by both hyperoxia and reactive oxygen species, thereby making the lungs more vulnerable to injury.[289]

Another factor which may explain both the adverse pulmonary sequelae but improved ophthalmic outcomes seen in infants targeted at a higher oxygen saturation level (see section 4.5) is the influence of vascular endothelial growth factor (VEGF). Hyperoxia-induced injury to the developing lung results in disordered vascular development. In animal models, during acute lung injury VEGF levels are markedly decreased but during post-injury recovery, up-regulation of VEGF accompanies the re-establishment of normal vasculature.[290] Similarly, in the first phase of ROP, exposure of the extremely preterm infant to the relatively hyperoxic extra-uterine environment after birth leads to down regulation of VEGF production and the cessation of normal blood vessel development in the retina.[100] A rebound overproduction of VEGF to compensate for the resulting tissue metabolic imbalance leads to the abnormal vascularisation typical of human ROP.[101] Hence it is plausible that the decrease in VEGF production seen in these infants during their initial lung and eye injury, followed by the up-regulation of VEGF in the recovery phase of both conditions, could explain the somewhat contradictory findings of adverse pulmonary sequelae but improved ophthalmic outcomes.

The only other two existing trials[88, 291] that have randomised preterm infants to target higher or lower blood oxygen levels (in these trials the measure of oxygenation was PaO_2) reported only one clinically important outcome, death. A Cochrane Systematic Review[87] showed that when the death outcomes from the two trials were meta-analysed, there was no statistically significant difference between the high and low PaO_2 groups (RR 0.91, 95% CI 0.57, 1.44; P=0.85). Synthesis of the results from the BOOST trial with this Cochrane review data would not be feasible as both of the included trials use the intervention in the first days of life when death rates would be expected to be high, rather than in the chronic phase of the infant's illness as applied in the BOOST trial when death rates would be expected to be quite low.

4.5 <u>Ophthalmic outcomes</u>

The BOOST trial was not designed to answer the question of the effect of higher oxygen targeting on ophthalmic outcomes, and as such did not have sufficient statistical power (only approximately 60%) to detect clinically meaningful differences in these secondary outcomes. The trial would have needed a sample size of approximately 570 infants (almost double its actual size) to assess ophthalmic outcomes reliably. However, the effect of differing oxygen saturation target ranges on ROP is of interest, as infants were randomised to the differing treatments at 32 weeks postmenstrual age before threshold ROP usually develops and as these were important clinical outcomes they were pre-specified as measures for analysis.

Current treatment for severe ROP (stage 3 or greater, known as threshold disease) is invasive and involves ablation of the avascular retina by cryotherapy or laser photocoagulation[101] as this form of therapy has been shown to reduce unfavourable ophthalmic outcomes by up to 50%.[292] However, even after this invasive treatment, retinal detachment and blindness still occur in some infants.[293] Retinal ablation is also not without complication, with iris atrophy, cataracts and hypotony being reported following this procedure.[294] A reduction in the need for this form of therapy would suggest that infants had less severe eye disease as they did not require this invasive treatment. When interpreting rates of ablative retinal surgery in the future, the results of the ongoing ET-ROP trial,[295] which is comparing ablative surgery prior to reaching threshold ROP with current practice, should be considered, as future rates may not be comparable with those of the current study.

Both STOP-ROP[106] and this trial suggest less ophthalmic intervention use when a higher oxygen saturation range is targeted in a sub-group of early gestation infants with more severe eye disease. Whilst not statistically significant, a difference in the rate of ablative retinal surgery in the BOOST trial of 16% in the standard range group compared with a rate of 8% in the higher oxygen group for infants less than 28 weeks' gestation at birth (see section 3.5.4) may be important information for clinicians weighing up the harms and benefits of the treatment. The rates of ablative surgery were not reported directly in the STOP-ROP trial. However, it can be assumed that virtually all infants reaching threshold ROP in that trial received ablative surgery treatment as this was the standard practice of the participating units

(personal communication: Dale Phelps, 2002). If this is the case, the STOP-ROP trial results also demonstrated a reduced need for ablative retinal surgery in infants targeted at a higher saturation range (48% in the standard group versus 41% in the higher group), although again this was not statistically significant.

Three early trials[87] and a recent UK cohort study[91] found that infants nursed at *lower* levels of oxygen or who were targeted at lower SpO_2 levels during the *early* weeks of life had significantly less severe eye disease. Both the STOP-ROP and BOOST trials randomised infants during the *chronic* phase of their oxygen dependency, after many of the factors that potentially contribute to the development of ROP have already occurred. The potentially beneficial effects of higher oxygen targeting in reducing the amount of ablative retinal surgery required for infants with severe ROP seen in both these trials, needs to be considered in the context of when during the course of the infant's illness the intervention was given. Hence the results of both the BOOST and STOP-ROP trials, which show some improved eye outcomes with higher oxygen targeting should not automatically be extrapolated to preterm infants of an earlier postnatal age.

The fact that there were no significant differences in the rates of severe ROP (stage 3 or greater) in this trial may have been a function of insufficient sample size for this secondary outcome analysis. As ophthalmic outcomes are clinically important, any new trial assessing the effects of differing oxygen saturation levels in the early weeks of life on the prevention of ROP should be designed with sufficient sample size to detect this outcome.[281]

4.6 Psychosocial outcomes

The trial was not resourced sufficiently to achieve follow-up rates for the secondary psychosocial outcomes of greater than the 71-77% achieved. This has implications for the interpretation of the results as it has been demonstrated that subjects who fail to participate in, or comply with treatment allocation or the follow-up regime within a trial have, on average, worse outcomes than trial participants in either the active or control arm of the study.[186]

However, the mean and median values for each scale (see section 3.5.5) were similar in the

trial infants to those reported with each instrument's normative data and/or when used in other populations of preterm infants.[191, 225, 230, 233, 235, 240] The mean Edinburgh Postnatal Depression Score (EPDS) and the proportion of women with elevated EDPS scores decreased over time as would be expected, although the high rate of elevated EDPS scores during the infant's initial hospitalisation (32% of mothers at 32 weeks pma) warrants consideration by clinicians caring for such families. The prior hypothesis that higher oxygen saturation targeting may result in infants with improved temperament who are thus less stressful for their families cannot be supported by the data from this trial.

4.7 <u>Health service utilisation and rehospitalisation outcomes</u>

As with the psychosocial outcomes, there were no significant differences between the two groups with regard to the use of health care services and rates of rehospitalisation in the first year of life (see section 3.5.6). The hypothesis that higher oxygen targeting results in a "healthier" infant cannot be supported by the data from this trial.

Both groups had very high use of health services during their first months at home: 28 and 31 visits per infant in the standard and higher groups respectively. This translates to, on average, more than one visit to a health care provider every fortnight. Similarly, rehospitalisation was quite common for these infants with more than half (51%) requiring at least one readmission to hospital during their first year of life. Despite the increased need for services and support, less than half of these high-risk infants were visited by a trained family support nurse, the use of which has been documented to decrease general practitioner visits, improve infant temperament and reduce maternal anxiety.[269]

The sub-group of infants receiving home oxygen therapy used health care services significantly more in the first year of life and were much more likely to require rehospitalisation (see section 3.5.6, Table 19). Our findings are consistent with other studies that have found increased health service needs for these particularly high risk infants.[19, 23, 284] These results should be noted by clinicians, considering that in this trial infants in the higher oxygen targeting group were 1.78 times more likely to receive home oxygen compared with infants in the standard group (see section 3.5.1).

CHAPTER 5: CONCLUSIONS

5.1 Implications for clinical practice

The results of this double-blind randomised trial show no evidence of growth or development benefits of targeting a functional oxygen saturation range of 95-98% compared with a range of 91-94% in chronically oxygen-dependent preterm infants.

The results of this randomised trial contradict much of the previously published observational evidence suggesting the benefits of routine higher oxygen targeting in chronically oxygen dependent, preterm infants. Based on the BOOST Trial results, for every 1,000 infants targeted at higher oxygen saturation levels, 183 additional infants would remain in oxygen at 36 weeks postmenstrual age and 131 more would be discharged on home oxygen. These potential health service costs come with no convincing evidence of growth or neurodevelopment benefits and thus, the routine use of higher oxygen targeting for chronically oxygen-dependent, preterm infants cannot be recommended.

The BOOST Trial addressed only the question of the effects of two different oxygen saturation target ranges in chronically oxygen-dependent, preterm infants. Hence, the results of this trial should not be extrapolated to practice recommendations for oxygen-dependent, preterm infants prior to 32 weeks postmenstrual age.

One of the major findings of the trial was the significantly increased rate of home oxygen therapy in the higher oxygen group. From information gained by extensive interaction with this group of high-risk infants by the research team, considerable variation was observed in the types of services and support provided by different centres, and the way in which those services were administered. There were no established models of post-discharge care that were

used by all centres. It is thus recommended that a coordinated, state-wide home oxygen service should be established to enhance equity of service provision in this area.

5.2 Implications for future research

Whilst this trial has helped answer the question of whether targeting a higher oxygen saturation range for chronically oxygen-dependent preterm infants is beneficial in the long-term, it has not resolved the question of the most appropriate oxygen saturation range for preterm infants in the early weeks of life. This important clinical question can only be answered in the context of further large, well-designed randomised trials with good long-term follow-up.[24] A collaborative group (including the author) has been formed to bring this idea to fruition.[281]

It is important that the results of the BOOST trial are applied in clinical practice. In addition to the initial survey of current practice prior to the commencement of the trial,[86] another survey of trial-participating centres was conducted following completion of the trial but prior to the public release of the results. This showed that clinicians remained in equipoise regarding the most appropriate oxygen saturation target range for oxygen-dependent preterm infants. A further survey of clinical practice is planned for 6-12 months following publication of the primary manuscript in a major peer-reviewed journal. The information gained from this survey will also assist the planning committee of the next oxygen saturation trial in assessing clinicians' uptake of research findings.

The other research translation project that is currently underway is the formulation of guidelines for oxygen weaning and titration based on the data and experience gained in this trial. There are very few published data regarding the best method of maintaining a specific oxygen saturation target range and/or how best to titrate oxygen in order to wean infants into air appropriately.[103, 104]

Finally, in the sub-group of home oxygen infants more research work is needed. Elucidating the impact of this therapy on families is currently being investigated by the author in collaboration with others using qualitative study methodologies. There are no randomised controlled trials that have addressed the question of whether infants requiring home oxygen (by whatever discharge criteria) grow and develop better if their oxygen saturation levels are targeted at a higher level after discharge, and whether such an intervention has any effects on other important secondary outcomes such as duration of home oxygen, infant temperament, parenting stress or family impact. This should be a priority for future research and would benefit from the collaboration of paediatric respiratory physicians, neonatologists and neonatal nurses.

REFERENCES

1.   Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990s. Seminars in Neonatology 2000; 5:89-106.

2.   Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. Archives of Pediatrics & Adolescent Medicine 1998; 152:425-435.

3.   Stevenson DK, Wright LL, Lemons JA, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. American Journal of Obstetrics & Gynecology 1998; 179:1632-1639.

4.   Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988; 82:527-532.

5.   Jobe AH, Bancalari E. Bronchopulmonary dysplasia. American Journal of Respiratory & Critical Care Medicine 2001; 163:1723-1729.

6.   Strangway A, Fowler R, Cunningham K, Hamilton JR. Diet and growth in congenital heart disease. Pediatrics 1976; 57:75-86.

7.   Sholler GF, Celermajer JM. Cardiac surgery in the first year of life: the effect on weight gains of infants with congenital heart disease. Australian Paediatric Journal 1986; 22:305-308.

8.   Vohr BR, Bell EF, Oh W. Infants with bronchopulmonary dysplasia. Growth pattern and neurologic and developmental outcome. American Journal of Diseases of Children 1982; 136:443-447.

9.   Meisels SJ, Plunkett JW, Roloff DW, Pasick PL, Stiefel GS. Growth and development of preterm infants with respiratory distress syndrome and bronchopulmonary dysplasia. Pediatrics 1986; 77:345-352.

10.   Sauve R, Singhal N. Long-term morbidity of infants with bronchopulmonary dysplasia. Pediatrics 1985; 76:725-733.

11. Yu VY, Orgill A, Lim S, Bajuk B, Astbury J. Growth and development of very low birthweight infants recovering from bronchopulmonary dysplasia. Archives of Disease in Childhood 1983; 58:791-794.

12. Markestad T, Fitzhardinge PM. Growth and development in children recovering from bronchopulmonary dysplasia. Journal of Pediatrics 1981; 98:597-602.

13. Landsborough L, Coenen A, De Bruecker J, Gurrin L, Evans S. Relationship between chronic lung disease, feeding behaviour and weight gain in the first year of life: a case-control study, Perinatal Society of Australia and New Zealand 4th Annual Congress, Brisbane, Australia, 2000. Wyeth Clinical Meetings Service.

14. Vohr BR, Coll CG, Lobato D, Yunis KA, O'Dea C, Oh W. Neurodevelopmental and medical status of low-birthweight survivors of bronchopulmonary dysplasia at 10 to 12 years of age. Developmental Medicine & Child Neurology 1991; 33:690-697.

15. Robertson CM, Etches PC, Goldson E, Kyle JM. Eight-year school performance, neurodevelopmental, and growth outcome of neonates with bronchopulmonary dysplasia: a comparative study. Pediatrics 1992; 89:365-372.

16. Skidmore MD, Rivers A, Hack M. Increased risk of cerebral palsy among very low-birthweight infants with chronic lung disease. Developmental Medicine & Child Neurology 1990; 32:325-332.

17. Hack M. School-age outcomes in children with birth weights under 750 grams. New England Journal of Medicine 1994; 331:753-759.

18. Gregoire MC, Lefebvre F, Glorieux J. Health and developmental outcomes at 18 months in very preterm infants with bronchopulmonary dysplasia. Pediatrics 1998; 101:856-860.

19. Chye JK, Gray PH. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. Journal of Paediatrics & Child Health 1995; 31:105-111.

20. Furman L, Baley J, Borawski-Clark E, Aucott S, Hack M. Hospitalization as a measure of morbidity among very low birth weight infants with chronic lung disease. Journal of Pediatrics 1996; 128:447-452.

21. Cunningham CK, McMillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. Pediatrics 1991; 88:527-532.

_____

22. Greenough A, Rafferty GF, Dimitriou G, et al. Home oxygen status and rehospitalisation and primary care requirements of infants with chronic lung disease. Transplantation 2002; 73:228-232.

23. Greenough A, Cox S, Alexander J, et al. Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. Archives of Disease in Childhood 2001; 85:463-468.

24. Tin W. Oxygen therapy: 50 years of uncertainty. Pediatrics 2002; 110:615-616.

25. Duc G, Sinclair JC. Oxygen administration. In: Effective Care Of the Newborn Infant. New York: Oxford University Press, 1992:178-198.

26. Bakwin H. Oxygen therapy in premature babies with anoxemia. American Journal of Diseases of Children 1923; 25:157-192.

27. Poets CF. When do infants need additional inspired oxygen? A review of the current literature. Pediatric Pulmonology 2001; 26:424-428.

28. Donoghue D. Report of the Australian and New Zealand Neonatal Network, 2000. Sydney: NSW Pregnancy and Newborn Services Network, University of Sydney, 2002:1-62.

29. Richard D, Poets CF, Neale S, Stebbens VA, Alexander JR, Southall DP. Arterial oxygen saturation in preterm neonates without respiratory failure. Journal of Pediatrics 1993; 123:963-968.

30. Poets CF, Stebbens VA, J.R. A, Arrowsmith WA, Salfield SAW, Southall DP. Arterial oxygen saturation in preterm infants at discharge from the hospital and six weeks later. Journal of Pediatrics 1992; 120:447-454.

31. O'Brien LM, Stebbens VA, Poets CF, Heycock EG, Southall DP. Oxygen saturation during the first 24 hours of life. Archives of Disease in Childhood: Fetal & Neonatal Edition 2000; 83:F35-F38.

32. Poets CF, Stebbens VA, Lang JA, O'Brien LM, Boon A, Southall DP. Arterial oxygen saturation in healthy term neonates. European Journal of Pediatrics 1996; 155.

33. Stebbens VA, Poets CF, J.R. A, Arrowsmith WA, Southall DP. Oxygen saturation and breathing patterns in infancy. I. Full term infants in the second month of life. Archives of Disease in Childhood 1991; 66:569-573.

34. Poets CF, Stebbens VA, Southall DP. Arterial oxygen saturation and breathing movements during the first year of life. Journal of Developmental Physio logy 1991; 15:341-345.

35. Koch G, Wendel H. Adjustment of arterial blood gases and acid base balance in the normal newborn infant during the first week of life. Biology of the Neonate 1968; 12:136-161.

36. Anonymous. Clinical considerations in the use of oxygen. In: Freeman RK, Poland RL, Hauth JC, Merenstein GB, eds. In: Guildlines for Perinatal Care. Evanston, Washington: American Academy of Pediatrics and American College of Obstetrics and Gynaecology, 1992:212-216.

37. Stahlman M, Shepard FM, Young WC, Gray J, Blakenship W. Assessment of the cardiovascular status of infants with hyaline membrane disease. In: Cassels DE, ed. In: The Heart and Circulation of the Newborn and Infant. New York: Grune & Stratton, 1966:121-140.

38. Murdock AI, Swyer PR. The contribution to venous admixture by shunting through the ductus arteriosus in infants with the respiratory distress syndrome of the newborn. Biologia Neonatorum 1968; 13:194-210.

39. Mike V, Krauss AN, Ross GS. Doctors and the health industry: a case study of transcutaneous oxygen monitoring in neonatal intensive care. Social Science & Medicine 1996; 42:1247-1258.

40. Yamanouchi I, Igarashi I, Ouchi E. Successful prevention of retinopathy of prematurity via transcutaneous oxygen partial pressure monitoring. In: Huch R, Huch A, eds. In: Consensus Blood Gas Monitoring. New York: Marcel Dekker, 1983:333-340.

41. Yamanouchi I, Igarashi I, Ouchi E. Incidence and severity of retinopathy in low birth weight infants monitored by TCPO2. Advances in Experimental Medicine & Biology 1987; 220:105-108.

42. Grylack LJ. Transcutaneous oxygen monitoring and retinopathy of prematurity. Pediatrics 1987; 80:973.

43. Bancalari E, Flynn J, Goldberg RN, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics 1987; 79:663-669.

44.   Flynn JT, Bancalari E, Bawol R, et al. Retinopathy of prematurity. A randomized, prospective trial of transcutaneous oxygen monitoring. Ophthalmology 1987; 94:630-638.

45.   Bancalari E, Flynn J, Goldberg RN, et al. Transcutaneous oxygen monitoring and retinopathy of prematurity. Advances in Experimental Medicine & Biology 1987; 220:109-113.

46.   Cunningham S, Fleck B, Elton R, McIntosh N. Transcutaneous oxygen levels in retinopathy of prematurity. Lancet 1995; 345:1464-1465.

47.   Mattia FR, deRegnier RA. Chronic physiologic instability is associated with neurodevelopmental morbidity at one and two years in extremely premature infants. Pediatrics 1998; 102:E35.

48.   Saito Y, T. O, Cho Y, Hatsukawa Y, Fujimura M, Takeuchi T. The progression of retinopathy of prematurity and fluctuation in blood gas tension. Graefes Archive for Clinical & Experimental Ophthalmology 1993; 231:151-156.

49.   Williams AJ. ABC of oxygen: assessing and interpreting arterial blood gases and acid-base balance. BMJ 1998; 317:1213-1216.

50.   Grace RF. Pulse oximetry. Gold standard or false sense of security? Medical Journal of Australia 1994; 160:638-644.

51.   Anonymous. Measurement of functional and fractional oxygen saturation: pulse oximetry note number 2. Haywood, California: Nellcor Incorporated, 1987.

52.   Foster J, Todd DA, Bidewell J, Askie LM. Pulse oximetry measures compared for neonates <28 weeks' gestation. Neonatal, Paediatric and Child Health Nursing 2002; 5:6-11.

53.   Thilo EH, Andersen D, Wasserstein ML, Schmidt J, Luckey D. Saturation by pulse oximetry: comparison of the results obtained by instruments of different brands. Journal of Pediatrics 1993; 122:620-626.

54.   Walsh MC, Noble LM, Carlo WA, Martin RJ. Relationship of pulse oximetry to arterial oxygen tension in infants. Critical Care Medicine 1987; 15:1102-1105.

55.   Deckardt R, Steward DJ. Noninvasive arterial hemoglobin oxygen saturation versus transcutaneous oxygen tension monitoring in the preterm infant. Critical Care Medicine 1984; 12:935-939.

56.	Southall DP, Bignall S, Stebbens VA, Alexander JR, Rivers RP, Lissauer T. Pulse oximeter and transcutaneous arterial oxygen measurements in neonatal and paediatric intensive care. Archives of Disease in Childhood 1987; 62:882-888.

57.	Cote CJ, Goldstein EA, Cote MA, Hoaglin DC, Ryan JF. A single-blind study of pulse oximetry in children. Anesthesiology 1988; 68:184-188.

58.	Bucher HU, Fanconi S, Baeckert P, Duc G. Hyperoxemia in newborn infants: detection by pulse oximetry. Pediatrics 1989; 84:226-230.

59.	Poets CF, Wilken M, Seidenberg J, Southall DP, von der Hardt H. Reliability of a pulse oximeter in the detection of hyperoxemia. Journal of Pediatrics 1993; 122:87-90.

60.	Cochran DP, Shaw NJ. The use of pulse oximetry in the prevention of hyperoxaemia in preterm infants. European Journal of Pediatrics 1995; 154:222-224.

61.	Guruprasad G, Kumar P, Narang A, Bhakoo ON. Usefulness of oxygen saturation (SpO2) monitoring in sick preterm neonates. Indian Pediatrics 1997; 34:131-132.

62.	Poets CF, Southall DP. Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. Pediatrics 1994; 93:737-746.

63.	Dear PR. Monitoring oxygen in the newborn: saturation or partial pressure? Archives of Disease in Childhood 1987; 62:879-881.

64.	Northway WH, Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. New England Journal of Medicine 1967; 276:357-368.

65.	Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA. Lung injury in neonates: causes, strategies for prevention, and long-term consequences. Journal of Pediatrics 2001; 139:478-486.

66.	Palta M, Sadek M, Barnet JH, et al. Evaluation of criteria for chronic lung disease in surviving very low birth weight infants. Newborn Lung Project. Journal of Pediatrics 1998; 132:57-63.

67.	Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. Journal of Pediatrics 1979; 95:819-823.

68.	Northway WH, Jr. Bronchopulmonary dysplasia: thirty-three years later. Pediatric Pulmonology 2001; Suppl 23:5-7.

69.	Davis PG, Thorpe K, Roberts R, et al. Evaluating "old" definitions for the "new" bronchopulmonary dysplasia. Journal of Pediatrics 2002; 140:555-560.

70.   Makhoul IR. Neonatal lung injury and "new BPD": need for a new terminology. Journal of Pediatrics 2002; 141:150.

71.   Egreteau L, Pauchard JY, Semama DS, et al. Chronic oxygen dependency in infants born at less than 32 weeks' gestation: incidence and risk factors. Pediatrics 2001; 108:E26.

72.   Hannaford K, Todd DA, Jeffery H, John E, Blyth K, Gilbert GL. Role of ureaplasma urealyticum in lung disease of prematurity. Archives of Disease in Childhood: Fetal & Neonatal Edition 1999; 81:F162-F167.

73.   Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987; 79:26-30.

74.   Korhonen P, Tammela O, Koivisto AM, Laippala P, Ikonen S. Frequency and risk factors in bronc hopulmonary dysplasia in a cohort of very low birth weight infants. Early Human Development 1999; 54:245-58.

75.   Crowley P. Corticosteroids prior to preterm delivery. Cochrane Database of Systematic Reviews 2002; Issue 4.

76.   Vaucher YE. Bronchopulmonary dysplasia: an enduring challenge. Pediatrics in Review 2002; 23:349-358.

77.   Schindler MB. Strategies to prevent chronic neonatal lung disease. Journal of Paediatrics & Child Health 1996; 32:477-479.

78.   Lyon A. The management of chronic lung disease. Current Paediatrics 2002; 12:7-12.

79.   Roze JC, Darmaun D, Gaultier C. Oxygen consumption in infants with bronchopulmonary dysplasia. Pediatric Pulmonology - Supplement 1997; 16:172-173.

80.   Sekar K, Duke JC. Sleep apnoea and hypoxaemia in recently weaned premature infants with and without bronchopulmonary dysplasia. Pediatric Pulmonology 1991; 10:112-116.

81.   Singer L. Oxygen desaturation complicates feeding in infants with bronchopulmonary dysplasia after discharge. Pediatrics 1992; 90:380-384.

82.   Simakajornboon N, Beckerman RC, Mack C, Sharon D, Gozal D. Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. Pediatrics 2002; 110:884-888.

83.   Harris MA, Sullivan CE. Sleep pattern and supplementary oxygen requirements in infants with chronic neonatal lung disease. Lancet 1995; 345:831-832.

84.   Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. American Journal of Diseases of Children 1987; 141:992-995.

85.   Hudak BB, Allen MC, Hudak ML, Loughlin GM. Home oxygen therapy for chronic lung disease in extremely low-birth-weight infants. American Journal of Diseases of Children 1989; 143:357-360.

86.   Kidd S, Henderson-Smart DJ. A survey of usual practice with respect to maintaining and monitoring oxygen saturation (SpO2) of chronically oxygen-dependent babies, Australian Perinatal Society Annual Conference, 1995. Wyeth Clinical Meetings Service.

87.   Askie LM, Henderson-Smart DJ. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2003; Issue 1.

88.   Usher RH. Treatment of respiratory distress syndrome. In: Winters RW, ed. In: The Body Fluids in Pediatrics. Boston, Toronto: Little Brown, 1973:303-337.

89.   Kinsey VE. Retrolental fibroplasia. Cooperative study of retrolental fibroplasia and the use of oxygen. Ophthalmology 1956; 56:481-543.

90.   Lanman TJ, Guy LP, Dancis J. Retrolental fibroplasia and oxygen therapy. JAMA 1954; 155:223-226.

91.   Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 84:F106-F110.

92.   Werthammer J, Brown ER, Neff R, Taeusch HW. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. Pediatrics 1982; 69:301-304.

93.   Gray PH, Rogers Y. Are infants with bronchopulmonary dysplasia at risk for sudden infant death syndrome. Pediatrics 1994; 93:774-777.

94.   Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. Pediatrics 1996; 98:779-783.

95.   Watts J. Retinopathy of prematurity. In: Sinclair J, Bracken M, eds. Effective Care of the Newborn Infant. Oxford: Oxford University Press, 1992:617-639.

96.   Cryotherapy for Retinopathy of Prematurity Cooperative Group. The natural ocular outcome of premature birth and retinopathy: status at 1 year. Archives of Ophthalmology 1994; 112:903-912.

97.   Laser ROP Study Group. Laser therapy for retinopathy of prematurity. Arch Ophthalmol 1994; 112:154-156.

98.   Reese AB, M. K, W.C. O. A classification of retrolental fibroplasia. Am J Ophthalmol 1953; 36:1333-1335.

99.   Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Archives of Ophthalmology 1988; 106:471-479.

100.   Pierce EA, Foley ED, Smith LE. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. Archives of Ophthalmology 1996; 114:1219-1228.

101.   Chan Ling T, Gock B, Stone J. Supplemental oxygen therapy: basis for noninvasive treatment of retinopathy of prematurity. Invest Ophthalmol Vis Sci 1995; 36:1215-1230.

102.   Phelps D. Reduced severity of oxygen-induced retinopathy in kittens recovered in 28% oxygen. Pediatric Research 1988; 24:106-109.

103.   Askie LM, Henderson-Smart DJ. Early versus late discontinuation of oxygen in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2002; Issue 4.

104.   Askie LM, Henderson-Smart DJ. Gradual versus abrupt discontinuation of oxygen in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2002; Issue 4.

105.   Flynn J, Bancalari E, Snyder E, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. NEJM 1992; 326:1050-1054.

106.   The STOP-ROP Multicenter Study Group. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 2000; 105:295-310.

107.   Kinsey V, Arnold H, Kalina R, et al. PaO2 levels and retrolental fibroplasia: a report of the cooperative study. Pediatrics 1977; 60:655-668.

108. Katzman G, Satish M, Krishnan V. Hypoxemia and retinopathy of prematurity. Pediatrics 1987; 80:972.

109. Gunn T, Easdown J, Outerbridge E, Aranda J. Risk factors in retrolental fibroplasia. Pediatrics 1980; 65:1096-1100.

110. Phelps D, Rosenbaum A. Effects of marginal hypoxemia on recovery from oxygen-induced retinopathy in the kitten model. Pediatrics 1984; 73:1-6.

111. Gaynon M, Stevenson D, Sunshine P, Fleisher B, Landers M. Supplemental oxygen may decrease progression of prethreshold disease to threshold retinopathy of prematurity. Journal of Perinatology 1997; 17:434-438.

112. Vrlenich LA, Bozynski ME, Shyr Y, Schork MA, Roloff DW, McCormick MC. The effect of bronchopulmonary dysplasia on growth at school age. Pediatrics 1995; 95:855-859.

113. Baraldi E, Carra S, Vencato F, et al. Home oxygen therapy in infants with bronchopulmonary dysplasia: a prospective study. European Journal of Pediatrics 1997; 156:878-882.

114. Murray AB, Fraser BM, Hardwick DF, Pirie GE. Chronic asthma and growth failure in children. Lancet 1976; 2:801-802.

115. Katz-Salamon M, Gerner EM, Jonsson B, Lagercrantz H. Early motor and mental development in very preterm infants with chronic lung disease. Archives of Disease in Childhood: Fetal & Neonatal Edition 2000; 83:F1-F6.

116. Gray PH, Burns YR, Mohay HA, O'Callaghan MJ, Tudehope DI. Neurodevelopmental outcome of preterm infants with bronchopulmonary dysplasia. Archives of Disease in Childhood: Fetal & Neonatal Edition 1995; 73:F128-F134.

117. Teberg AJ, Pena I, Finello K, Aguilar T, Hodgman JE. Prediction of neurodevelopmental outcome in infants with and without bronchopulmonary dysplasia. American Journal of the Medical Sciences 1991; 301:369-374.

118. Lifschitz MH, Seilheimer DK, Wilson GS, Williamson WD, Thurber SA, Desmond MM. Neurodevelopmental status of low birth weight infants with bronchopulmonary dysplasia requiring prolonged oxygen supplementation. Journal of Perinatology 1987; 7:127-132.

119. Goldson E. Severe bronchopulmonary dysplasia in the very low birth weight infant: its relationship to developmental outcome. Journal of Developmental & Behavioral Pediatrics 1984; 5:165-168.

120. Tammela OK, Koivisto ME. A 1-year follow-up of low birth weight infants with and without bronchopulmonary dysplasia: health, growth, clinical lung disease, cardiovascular and neurological sequelae. Early Human Development 1992; 30:109-120.

121. Scher MS, Richardson GA, Salerno DG, Day NL, Guthrie RD. Sleep architecture and continuity measures of neonates with chronic lung disease. Sleep 1992; 15:195-201.

122. Fitzgerald D, Van Asperen P, O'Leary P, et al. Sleep, respiratory rate, and growth hormone in chronic neonatal lung disease. Pediatric Pulmonology 1998; 26:241-249.

123. Fitzgerald D, Van Asperen P, Leslie G, Arnold J, Sullivan C. Higher SaO2 in chronic neonatal lung disease: does it improve sleep? Pediatric Pulmonology 1998; 26:235-240.

124. Zinman R, Blanchard, Vachon. Oxygen saturation during sleep in patients with bronchopulmonary dysplasia. Biol Neonate 1992; 61:69-75.

125. Haider AZ, Rehan V, Alvaro R, et al. Low baseline oxygenation predisposes preterm infants to mixed apneas during inhalation of 100% oxygen. American Journal of Perinatology 1996; 13:363-369.

126. Rigatto H. Apnea. Pediatric Clinics of North America 1982; 29:1105-1116.

127. Rigatto H. Periodic breathing and apnea in preterm infants. II. Hypoxia as a primary event. Pediatrics 1972; 50:219-228.

128. Weinstein MR, Oh W. Oxygen consumption in infants with bronchopulmonary dysplasia. Journal of Pediatrics 1981; 99:958-961.

129. Kao LC, Durand DJ, Nickerson BG. Improving pulmonary function does not decrease oxygen consumption in infants with bronchopulmonary dysplasia. Journal of Pediatrics 1988; 112:616-621.

130. Schulze A, Abubakar K, Gill G, Way RC, Sinclair J. Pulmonary oxygen consumption: a hypothesis to explain the increase in oxygen consumption of low birth weight infants with lung disease. Intensive Care Medicine 2001; 27:1636-1642.

131. Garg M, Kurzner SI, Bautista DB, Keens TG. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. Pediatrics 1988; 81:635-642.

132. Bard H, Belanger S, Fouron J. Comparing a haemoglobin oxygen saturation of 95% vs 90% on the pulmonary circulatory hemodynamics of preterm infants with respiratory distress syndrome, American Pediatric Association, April 1994, 1994.

133. Dudell G, Cornish JD, Bartlett RH. What constitutes adequate oxygenation? Pediatrics 1990; 85:39-41.

134. McEvoy C, Durand M, Hewlett V. Episodes of spontaneous desaturations in infants with chronic lung disease at two different levels of oxygenation. Pediatric Pulmonology 1993; 15:140-144.

135. Samuels MP, Poets CF, Southall DP. Abnormal hypoxemia after life-threatening events in infants born before term. Journal of Pediatrics 1994; 125:441-446.

136. Iles R, Edmunds AT. Assessment of pulmonary function in resolving chronic lung disease of prematurity. Archives of Disease in Childhood: Featl Neonatal edition 1997; 76:F113-F117.

137. Parkins KJ, Poets CF, O'Brien LM, Stebbens VA, Southall DP. Effect of exposure to 15% oxygen on breathing patterns and oxygen saturation in infants: interventional study. BMJ 1998; 316:887-891.

138. Teague WG, Pian MS, Heldt GP, Tooley WH. An acute reduction in the fraction of inspired oxygen increases airway constriction in infants with chronic lung disease. American Review of Respiratory Disease 1988; 137:861-865.

139. Tay-Uyboco JS, Kwiatkowski K, Cates DB, Kavanagh L, Rigatto H. Hypoxic airway constriction in infants of very low birth weight recovering from moderate to severe bronchopulmonary dysplasia. Journal of Pediatrics 1989; 115:456-459.

140. Giacoia GP, Venkataraman PS, West-Wilson KI, Faulkner MJ. Follow-up of school-age children with bronchopulmonary dysplasia. Journal of Pediatrics 1997; 130:400-408.

141. Jacob SV, Lands LC, Coates AL, et al. Exercise ability in survivors of severe bronchopulmonary dysplasia. American Journal of Respiratory & Critical Care Medicine 1997; 155:1925-1929.

142. Fitzgerald DA, Mesiano G, Brosseau L, Davis GM. Pulmonary outcome in extremely low birth weight infants. Pediatrics 2000; 105:1209-1215.

143. Schulze A, Whyte RK, Way RC, Sinclair JC. Effect of the arterial oxygenation level on cardiac output, oxygen extraction, and oxygen consumption in low birth weight infants receiving mechanical ventilation. Journal of Pediatrics 1995; 126:777-784.

144. Bard H, Belanger S, Fouron JC. Comparison of effects of 95% and 90% oxygen saturations in respiratory distress syndrome. Archives of Disease in Childhood Fetal & Neonatal Edition 1996; 75:F94-F96.

145. Subhedar NV, Primhak RA, Shaw NJ. Pulmonary artery pressure: early predictor of chronic lung disease in preterm infants. Archives of Disease in Childhood: Fetal & Neonatal Edition 1998; 789:F20-F24.

146. Subhedar NV, Shaw NJ. Changes in pulmonary arterial pressure in preterm infants with chronic lung disease. Archives of Disease in Childhood: Fetal & Neonatal Edition 2000; 82:F243-F247.

147. Evans NJ, Archer LN. Doppler assessment of pulmonary artery pressure during recovery from hyaline membrane disease. Archives of Disease in Childhood 1991; 66:802-804.

148. Fitzgerald D, Evans N, Van Asperen P, Henderson-Smart D. Subclinical persisting pulmonary hypertension in chronic neonatal lung disease. Archives of Disease in Childhood Fetal & Neonatal Edition 1994; 70:F118-F122.

149. Gill AB, Weindling AM. Raised pulmonary artery pressure in very low birthweight infants requiring supplemental oxygen at 36 weeks after conception. Archives of Disease in Childhood Fetal & Neonatal Edition 1995; 72:F20-F22.

150. Halliday HL, Dumpit FM, Brady JP. Effects of inspired oxygen on echocardiographic assessment of pulmonary vascular resistance and myocardial contractility in bronchopulmonary dysplasia. Pediatrics 1980; 65:536-540.

151. Abman SH, Wolfe RR, Accurso FJ, Koops BL, Bowman CM, Wiggins JW, Jr. Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. Pediatrics 1985; 75:80-84.

152. James LS, Rowe RD. The pattern of response of pulmonary and systemic aterial pressures in newborn and older infants to short periods of hypoxia. Journal of Pediatrics 1957; 51:5-11.

153. Doyle LW, Cheung MMH, Ford GW, Olinsky A, David NM, Callanon C. Birth weight <1501 g and respiratory health at age 14. Archives of Disease in Childhood 2001; 84:40-44.

154. Les Chermignonards De'senchant'es. Oxygen and retrolental fibroplasia: the questions persist. Pediatrics 1977; 60:753-754.

155. Ellsbury DL, Acarregui MJ, McGuinness GA, Klein JM. Variability in the use of supplemental oxygen for bronchopulmonary dysplasia. Journal of Pediatrics 2002; 140:247-249.

156. Solis A, Harrison G, Shaw B. Assessing oxygen requirements after discharge in chronic lung disease: a survey of current practice. European Journal of Pediatrics 2002; 161:428-430.

157. Vijayakumar E, Ward GJ, Bullock CE, Patterson ML. Pulse oximetry in infants of <1500 gm birth weight on supplemental oxygen: a national survey. Journal of Perinatology 1997; 17:341-345.

158. McIntosh N, Marlow N. High or low oxygen saturation for the preterm baby. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 84:F149-F150.

159. Kotecha S, Allen J. Oxygen therapy for infants with chronic lung disease. Archives of Disease in Childhood: Fetal & Neonatal Edition 2002; 87:F11-F14.

160. Saugstad OD. Chronic lung disease: oxygen dogma revisited. Acta Paediatrica 2001; 90:113-115.

161. Saugstad OD. Is oxygen more toxic than currently believed? Pediatrics 2001; 108:1203-1205.

162. Primhak R. Oxygen saturation and retinopathy of prematurity. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 85:F75.

163. Tin W, Milligan D, Pennefather P. Oxygen saturation and retinopathy of prematurity - author's response. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 85:F75.

164. Roberton N. Two sacred cows of neonatal intensive care. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 85:F75-F76.

165. Hey E. Two sacred cows of neonatal intensive care - author's response. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 85:F75-F76.

166. Moher D, Schulz KF, Altman DG, Consort G. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Annals of Internal Medicine 2001; 134:657-662.

167. NSW NICU Study Group. New South Wales Neonatal Intensive Care Units Data Collection 1992-1993. Sydney: NSW Health Department, 1997.

168. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. Journal of Chronic Disease 1967; 20:637-648.

169. Masters IB, Asher MI. Domiciliary oxygen therapy in children. Journal of Paediatrics and Child Health 1993; 29:259-262.

170. Silva DT, Hagan R, Sly PD. Home oxygen management of neonatal chronic lung disease in Western Australia. Journal of Paediatrics & Child Health 1995; 31:185-188.

171. Peto R, Baigent C. Trials: the next 50 years. Large scale randomised evidence of moderate benefits. BMJ 1998; 317:1170-1171.

172. Buck GM, Msall ME, Schisterman EF, Lyon NR, Rogers BT. Extreme prematurity and school outcomes. Paediatric & Perinatal Epidemiology 2000; 14:324-331.

173. Anonymous. An international classification of retinopathy of prematurity. Pediatrics 1984; 74:127-133.

174. Anonymous. Technology overview: Nellcor Symphony N-3000 - the next generation in Nellcor Pulse Oximetry. Hayward, California: Nellcor Incoporated, 1994.

175. Simes RJ. Clinical trials and "real world" medicine. Medical Journal of Australia 2002; 177:410-411.

176. Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ, Callaghan T. Dynamic balanced randomization for clinical trials. Statistics in Medicine 1993; 12:2343-350.

177. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273:408-412.

178. Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. JAMA 1994; 272:125-128.

179. Schulz KF. Subverting randomization in controlled trials. JAMA 1995; 274:1456-1458.

180. Sinclair JC. Assessing evidence concerning treatment and prevention of diseases of the newborn. In: Sinclair JC, Bracken MB, eds. Effective care if the newborn infant. Oxford: Oxrod University Press, 1992:3-12.

181. Diehl LF, Perry DJ. A comparison of randomized concurrent control groups with matched historial control groups: Are historical controls valid? Journal of Clinical Oncology 1986; 4:1114-1120.

182. Wager E, Tooley PJH, Emanuel MB, Wood SF. How to do it. Get patients' consent to enter clinical trials. BMJ 1995; 311:734-737.

183. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. Journal of the American College of Cardiology 1996; 27:1335-1342.

184. Davis S, Wright PW, Schulman SF, et al. Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer 1985; 56:1710-1718.

185. Schmidt B, Gillie P, Caco C, Roberts J, Roberts R. Do sick newborn infants benefit from participation in a randomized clinical trial? Journal of Pediatrics 1999; 134:151-155.

186. Clemens JD, van Loon FF, Rao M, et al. Nonparticipation as a determinant of adverse health outcomes in a field trial of oral cholera vaccines. American Journal of Epidemiology 1992; 135:865-874.

187. Smith P, Arnesen H. Mortality in non-consenters in a post-myocardial infarction trial. Journal of Internal Medicine 1990; 228:253-256.

188. Anonymous. New South Wales Mothers and Babies 2000. NSW Public Health Bulletin Supplement, Volume 12, Number S-3. Sydney: NSW Health, 2001.

189. Murray L, Stein A. Postnatal depression and infant development. BMJ 1991; 302:978-979.

190. Murray L, Kempton C, Woolgar M, Hooper R. Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. Journal of Child Psychology & Psychiatry & Allied Disciplines 1993; 34:1083-1101.

191. Cox J, Holden J, Sagovsky R. Detection of Postnatal Depression. Development of the 10-item Edinburgh Postnatal Depression Scale. British Journal of Psychiatry 1987; 150:782-786.

192. Daniel AE. Power, privilege and prestige: occupations in Australia. Melbourne: Logman Cheshire, 1983.

193. Farrell B. Efficient management of randomised trials: nature or nuture. BMJ 1998; 317:1236-1239.

194. Kramer MS, Shapiro SH. Scientific challenges in the application of randomized trials. JAMA 1984; 252:2739-2745.

195. Vermeulen MJ, Weening FT, Battistutta D, Masters IB. Awake daytime oximetry measurements in the management of infants with chronic lung disease. Journal of Paediatrics & Child Health 1999; 35:553-557.

196. Bower LK, Barnhart SL, Betit P, Czervinske MP, Heulitt MJ, Wilson BG. Selection of an oxygen delivery device for neonatal and pediatric patients. Respiratory Care 1996; 41:637-646.

197. Whitelaw A, Thoresen M. Antenatal steroids and the developing brain. Archives of Disease in Childhood: Fetal & Neonatal Edition 2000; 83:F154-F157.

198. Schulpen TW, van Steenbergen JE, van Driel HF. Influences of ethnicity on perinatal and child mortality in the Netherlands. Archives of Disease in Childhood 2001; 84:222-226.

199. Teranishi H, Nakagawa H, Marmot M. Social class difference in catch up growth in a national British cohort. Archives of Disease in Childhood 2001; 84:218-221.

200. Horwood LJ, Darlow BA, Mogridge N. Breast milk feeding and cognitive ability at 7-8 years. Archives of Disease in Childhood: Fetal & Neonatal Edition 2001; 84:F23-F27.

201. Hamill PV. NCHS Growth Curves for Children Birth-18 years United States. Hyattsville, Maryland: National Center for Health Statistics, 1977.

202. Peralta-Carcelen M, Jackson DS, Goran MI, Royal SA, Mayo MS, Nelson KG. Growth of adolescents who were born at extremely low birth weight without major disability. Journal of Pediatrics 2000; 136:633-640.

203. Kitchen WH, Ford GW, Doyle LW. Growth and very low birth weight. Archives of Disease in Childhood 1989; 64:379-382.

204. Doyle LW. Growth and respiratory health in adolescence of the extremely low-birth weight survivor. Clinics in Perinatology 2000; 27:421-432.

205. Ford GW, Doyle LW, Davis NM, Callanan C. Very low birth weight and growth into adolescence. Archives of Pediatrics & Adolescent Medicine 2000; 154:778-784.

206.   Griffiths R, Huntley M. The Griffiths Mental Development Scales from birth to 2 years, Manual, the 1996 revision. Henley-on-Thames: The Test Agency Limited, 1996.

207.   Doyle LW. Outcome to five years of age of children born at 24-26 weeks' gestational age in Victoria. The Victorian Infant Collaborative Study Group. Med J Aust 1995; 163:11-14.

208.   Kitchen W, Ford G, Orgill A, et al. Outcome in infants of birth weight 500 to 999 g: a continuing regional study of 5-year-old survivors. Journal of Pediatrics 1987; 111:761-766.

209.   Luiz DM, Foxcroft CD, Stewart R. The construct validity of the Griffiths Scales of Mental Development. Child: Care, Health & Development 2001; 27:73-83.

210.   Ramsay M, Fitzhardinge P. A comparative study of two developmental scales: the Bayley and the Griffiths. Early Human Development 1977; 1:151-157.

211.   Bowen JR, Gibson FL, Leslie GI, Arnold JD, Ma PJ, Starte DR. Predictive value of the Griffiths assessment in extremely low birthweight infants. Journal of Paediatrics & Child Health 1996; 32:25-30.

212.   Largo RH, Graf S, Kundu S, Hunziker U, Molinari L. Predicting developmental outcome at school age from infant tests of normal, at-risk and retarded infants. Developmental Medicine & Child Neurology 1990; 32:30-45.

213.   Kohlhauser C, Fuiko R, Panagl A, et al. Outcome of very-low-birth-weight infants at 1 and 2 years of age. The importance of early identification of neurodevelopmental deficits. Clinical Pediatrics 2000; 39:441-449.

214.   Harris SR. Early detection of cerebral palsy: sensitivity and specificity of two motor assessment tools. Journal of Perinatology 1987; 7:11-15.

215.   Harris SR. Early neuromotor predictors of cerebral palsy in low-birthweight infants. Developmental Medicine & Child Neurology 1987; 29:508-519.

216.   Thompson CM, Buccimazza SS, Webster J, Malan AF, Molteno CD. Infants of less than 1250 grams birth weight at Groote Schuur Hospital: outcome at 1 and 2 years of age. Pediatrics 1993; 91:961-968.

217.   Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Developmental Medicine & Child Neurology 2000; 42:53-60.

218.   Anonymous. The International Classification of Diseases, 9th edition, Clinical Modification. US National Center for Health Statistics. Michigan: Edwards Brothers Incorporated, 1989.

219.   Kaiser RS, Trese MT. Iris atrophy, cataracts, and hypotony following peripheral ablation for threshold retinopathy of prematurity. Archives of Ophthalmology 2001; 119:615-7.

220.   Kurstjens S, Wolke D. Effects of maternal depression on cognitive development of children over the first 7 years of life. Journal of Child Psychology & Psychiatry & Allied Disciplines 2001; 42:623-636.

221.   Galler JR, Harrison RH, Ramsey F, Forde V, Butler SC. Maternal depressive symptoms affect infant cognitive development in Barbados. Journal of Child Psychology & Psychiatry & Allied Disciplines 2000; 41:747-757.

222.   Kratochvil MS, Robertson CM, Kyle JM. Parents' view of parent-child relationship eight years after neonatal intensive care. Social Work in Health Care 1991; 16:95-118.

223.   Fooks J, Mutch L, Yudkin P, Johnson A, Elbourne D. Comparing two methods of follow up in a multicentre randomised trial. Archives of Disease in Childhood 1997; 76:369-376.

224.   Boyce P, Stubbs J, Todd A. The Edinburgh Postnatal Depression Scale: validation for an Australian sample. Australian & New Zealand Journal of Psychiatry 1993; 27:472-476.

225.   Hagan R, Pope S, Evans S, Priest S, Rooney R, Sharp J. Maternal depression following preterm birth. Prenatal and Neonatal Medicine 1996; 1 (Suppl 1):129-132.

226.   Carey WB. A simplified method for measuring infant temperament. Journal of Pediatrics 1970; 77:188-194.

227.   Carey WB, McDevitt SC. Revision of the Infant Temperament Questionnaire. Pediatrics 1978; 61:735-739.

228.   Oberklaid F, Prior M, Golvan D, Clements A, Williamson A. Temperament in Australian infants. Australian Paediatric Journal 1984; 20:181-184.

229.   Sewell J, Oberklaid F. Temperament in infants and young children. Aust Paediatr. J 1986; 22:91-94.

230.   Oberklaid F, Prior M, Nolan T, Smith P, Flavell H. Temperament in infants born prematurely. Developmental & Behavioral Pediatrics 1985; 6:57-61.

231. Fullard W, McDevitt SC, Carey WB. Assessing temperament in one- to three-year-old children. Journal of Pediatric Psychology 1984; 9:205-217.

232. Prior M, Sanson A, Oberklaid F, Northam E. Measurement of temperament in one to three year old children. International Journal of Behaviour & Development 1987; 10:121-132.

233. Sewell J, Oberklaid F, Prior M, Sanson A, Kyrios M. Temperament in Australian toddlers. Australian Paediatric Journal 1988; 24:343-345.

234. Stein RE, Riessman CK. The development of an impact-on-family scale: preliminary findings. Medical Care 1980; 18:465-472.

235. Lee SK, Penner PL, Cox M. Impact of very low birth weight infants on the family and its relationship to parental attitudes. Pediatrics 1991; 88:105-109.

236. McCormick MC, Stemmler MM, Bernbaum JC, Farran AC. The very low birth weight transport goes home: impact on the family. Journal of Developmental & Behavioral Pediatrics 1986; 7:217-223.

237. Anonymous. Parenting Stress Index - short form. Odessa: Psychological Assessment Resources Incorporated, 1995.

238. Abidin RR. Parenting Stress Index: a measure of the parent-child system. In: Zalaquett CP, Woods RJ, eds. Evaluating stress: a book of resources. Lanham: Scarecrow Press, 1997:277-291.

239. Goldberg S, Morris P, Simmons RJ, Fowler RS, Levison H. Chronic illness in infancy and parenting stress: a comparison of three groups of parents. Journal of Pediatric Psychology 1990; 15:347-358.

240. Ong LC, Chandran V, Boo NY. Comparison of parenting stress between Malaysian mothers of four-year-old very low birthweight and normal birthweight children. Acta Paediatrica 2001; 90:1464-1469.

241. Saigal S, Rosenbaum P, Stoskopf B, et al. Comprehensive assesment of the health status of the extremelly low birth weight children at eight years of age: Comparison with a reference group. Peadriatrics 1994; 125:411-417.

242. Jackson K, Schollin J, Bodin L, Ternestedt BM. Utilization of healthcare by very-low-birthweight infants during their first year of life. Acta Paediatrica 2001; 90:213-217.

243. Lindeke LL, Mills MM, Georgieff MK, Tanner ME, Wrbsky PM. Health, growth, and use of community services in NICU graduates at early school age. Journal of Pediatric Health Care 1998; 12:299-304.

244. Lindeke LL, Stanley JR, Else BS, Mills MM. Neonatal predictors of school based services used by NICU graduates at school age. Journal of Maternal and Child Nursing 2002; 27:41-46.

245. Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Hospital admissions in the first year of life in very preterm infants. Journal of Paediatrics & Child Health 1999; 35:145-150.

246. Chien YH, Tsao PN, Chou HC, Tang JR, Tsou KI. Rehospitalization of extremely-low-birth-weight infants in first 2 years of life. Early Human Development 2002; 66:33-40.

247. McGuire TE, Bender JA. Australian national diagnosis groups (AN-DRGs). Vol. 2. Canberra: Australian Government Publishing Service, 1995.

248. National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: Biotext, 2000:23.

249. Wright JG. The minimal important difference: who's to say what is important? Journal of Clinical Epidemiology 1996; 49:1221-1222.

250. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998; 316:690-693.

251. Detsky AS, Sackett DL. When was a "negative" clinical trial big enough? How many patients you needed depends on what you found. Arch Intern Med 1985; 145:709-712.

252. Walter S. The Statistician 1979; 28:218-222.

253. Winkelstein W, Shillitoe EJ, Brand R, Johnson KK. Further comments on cancer of the uterine cervix, smoking and herpesvirus infection. Am J Epidemiol 1984; 119:1-8.

254. Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000; 355:1064-1069.

255. Hawkins BS. Data monitoring committees for multicenter clinical trials sponsored by the National Institutes of Health. I. Roles and membership of data monitoring committees for trials sponsored by the National Eye Institute. Controlled Clinical Trials 1991; 12:424-437.

256. Pocock SJ. Statistical and ethical issues in monitoring clinical trials. Statistics in Medicine 1993; 12:1459-1469; discussion 1471-1475.

257. Wittes J. Behind closed doors: the data monitoring board in randomized clinical trials. Statistics in Medicine 1993; 12:419-424.

258. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-556.

259. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Annals of Internal Medicine 2001; 134:663-694.

260. Altman DG, Dore CJ. Randomisation and baseline comparisons in clinical trials. Lancet 1990; 335:149-153.

261. Antman K, Amato D, Wood W, et al. Selection bias in clinical trials. Journal of Clinical Oncology 1985; 3:1142-1147.

262. Marcus SM. Assessing non-consent bias with parallel randomized and nonrandomized clinical trials. Journal of Clinical Epidemiology 1997; 50:823-828.

263. Charlson ME, Horwitz RI. Applying results of randomised trials to clinical practice: impact of losses before randomisation. British Medical Journal Clinical Research Ed. 1984; 289:1281-1284.

264. Bucher HU, Keel M, Wolf M, von Siebenthal K, Duc G. Artifactual pulse-oximetry estimation in neonates. Lancet 1994; 343:1135-1136.

265. Bayley N. Bayley Scales of Infant Development Manual. New York: The Psychological Coporation, 1969.

266. Ho JJ, Amar HS, Mohan AJ, Hon TH. Neurodevelopmental outcome of very low birth weight babies admitted to a Malaysian nursery. Journal of Paediatrics & Child Health 1999; 35:175-180.

267. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology. A basic science for clinical medicine. Boston, Toronto, London: Little, Brown and Company, 1991.

268. McLean A, Townsend A, Clark J, et al. Quality of life of mothers and families caring for preterm infants requiring home oxygen therapy: a brief report. Journal of Paediatrics & Child Health 2000; 36:440-444.

269.   Rieger ID, Henderson-Smart DJ. A neonatal early discharge and home support programme: shifting the care into the community. Journal of Paediatrics and Child Health 1995; 31:33-37.

270.   Aurelius G, Nordberg L. Home visiting to families with a newborn child. Scandinavian Journal of Primary Health Care - Supplement 1994; 12:106-113.

271.   Sauve RS, McMillan DD, Mitchell I, Creighton D, Hindle NW, Young L. Home oxygen therapy. Outcome of infants discharged from NICU on continuous treatment. Clinical Pediatrics 1989; 28:113-118.

272.   Abman SH, Accurso FJ, Koops BL. Experience with home oxygen in the management of infants with bronchopulmonary dysplasia. Clinical Pediatrics 1984; 23:471-476.

273.   Young LY, Creighton DE, Sauve RS. The needs of families of infants discharged home with continuous oxygen therapy. JOGNN 1987; May/June:187-193.

274.   Miller JN, Colditz GA, Mosteller F. How study design affects outcomes in comparisons of therapy. II: Surgical. Statistics in Medicine 1989; 8:455-466.

275.   Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. Statistics in Medicine 1989; 8:441-454.

276.   Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ 1998; 317:1185-1190.

277.   Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Annals of Internal Medicine 1996; 125:605-613.

278.   Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999; 282:786-790.

279.   Begg CB, Leung DHY. On the use of surrogate endpoints in randomized trials. Journal of the Royal Statistical Society 2000; 163:15-28.

280.   Gosselin J, Amiel-Tison C, Infante-Rivard C, Fouron C, Fouron JC. Minor neurological signs and developmental performance in high risk children at preschool age. Developmental Medicine & Child Neurology 2002; 44:323-328.

281.   Cole C, Tarnow-Mordi WO. Personal communication. Commentary for Pediatrics: resolving our uncertainty about oxygen therapy, 2002.

282.   Newcombe RG. Explanatory and pragmatic estimates of the treatment effect when deviations from allocated treatment occur. Statistics in Medicine 1988; 7:1179-1186.

283. Ministerial Neonatal Services Working Party. Neonatal Services in NSW. North Sydney: NSW Department of Health Services Development Branch, 1990:47-57.

284. Greenough A, Yuksel B, Page A, Karani J. Home oxygen therapy following neonatal intensive care. Early Human Development 1991; 26:37-43.

285. Gill A. Report of the NSW home oxygen working party. Sydney: Perinatal Service Network, 1993.

286. Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. Pharmacological Reviews 1971; 23:37-133.

287. Saugstad OD. Hypoxanthine as an indicator of hypoxia: its role in health and disease through free radical production. Pediatric Research 1988; 23:143-150.

288. Sullivan JL. Iron, plasma antioxidants, and the 'oxygen radical disease of prematurity'. American Journal of Diseases of Children 1988; 142:1341-1344.

289. Saugstad OD. Bronchopulmonary dysplasia and oxidative stress: are we closer to an understanding of the pathogenesis of BPD? Acta Paediatrica 1997; 86:1277-1282.

290. D'Angio CT, Maniscalco WM. The role of vascular growth factors in hyperoxia-induced injury to the developing lung. Frontiers in Bioscience 2002; 7:d1609-1623.

291. Sinclair JC, Engel K, Silverman WA. Early correction of hypoxaemia and acidemia in infants of low birth weight. A controlled trial of oxygen breathing, rapid alkali infusion and assisted ventilation. Pediatrics 1968; 42:565-589.

292. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: one-year outcome - structure and function. Archives of Ophthalmology 1990; 108:1408-1409.

293. Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO. Supplemental oxygen for the treatment of prethreshold retinopathy of prematurity (protocol). The Cochrane Library. Oxford: Update Software, 2002: Issue 3.

294. Kaiser RS, Trese MT. Iris atrophy, cataracts, and hypotony following peripheral ablation for threshold retinopathy of prematurity. Archives of Ophthalmology 2001; 119:615-617.

295. Good WV, Hardy RJ. The multicenter study of Early Treatment for Retinopathy of Prematurity (ETROP). Ophthalmology 2001; 108:1013-1014.

_____

APPENDICES

1. Research personnel

2. Study sites

3. Sample consent form and parent information sheet

4. Enrolment form

5. Sample trial promotional material

6. Downloading data collection sheet

7. Clinical data collection form

8. 4 month growth measures form

9. 12 month data collection form

10. Death report form

11. Retinopathy of Prematurity screening report form

12. Edinburgh Postnatal Depression Scale form

13. Infant Temperament Scale form

14. Toddler Temperament Scale form

15. Impact on Family Scale form

16. Parenting Stress Index form

17. Health service utilisation data collection form

18. Rehospitalisation form

19. Sample size calculations

20. Safety Monitoring Committee report form

21. Selected clinical outcomes adjusted for known prognostic factors

22. Major outcomes stratified by centre

23. Sensitivity analysis for effect of sibling pairs

24. List of published papers and abstracts

RESEARCH PERSONNEL:

Chief Investigators:
- Professor David Henderson-Smart (DHS), Director and Professor, NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-7318, fax (02) 9351-7742, pager 132222 No. 2883, email: dhs@perinatal.usyd.edu.au

- Professor Les Irwig (LI), Professor of Epidemiology, School of Public Health, University of Sydney, NSW 2006, phone (02) 9351-4370, fax (02) 9351-7420, email: lesi@health.usyd.edu.au

- Associate Professor Judy Simpson (JMS), Associate Professor (Biostatistics), School of Public Health, University of Sydney, NSW 2006, phone (02) 9351-4369, fax (02) 9351-7420, email: judys@health.usyd.edu.au

Associate Investigators:
- Mr Alan Shiell, Senior Lecturer (Health Economics), Department of Public Health and Community Medicine, University of Sydney, NSW 2006, phone (02) 9351-5127.

- Professor Frank Billson, Professor of Ophthalmology, Department of Ophthalmology, University of Sydney, NSW 2006, phone (02) 9351-3460.

- Dr Lee Sutton, Director, Neonatal Intensive Care Unit Study, NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-7750.

Study Coordinator and Coordinating Centre:
- Ms Lisa Askie (LMA), NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-7739, fax (02) 9351-7742, mobile 0410 570 735, email: lisa.askie@perinatal.usyd.edu.au

Research Nurses:
- Ms Rachel Jones, NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-4660, fax (02) 9351-7742, pager (02) 9963 3540, email: rachel.jones@perinatal.usyd.edu.au

- Ms Kim Smith, NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-7752, fax (02) 9351-7742, pager (02) 9963 3540, email: kim.smith@perinatal.usyd.edu.au

- Ms Vicki Geeves, NSW Centre for Perinatal Health Services Research, Building D02, University of Sydney, NSW 2006, phone (02) 9351-7752, fax (02) 9351-7742, pager (02) 9963 3540, email: vicki.geeves@perinatal,.usyd.edu.au

Study sites and nominated liaison representatives:

- Canberra Hospital, Woden Valley, ACT: Prof Graham Reynolds (medical); Ms Heather Cox (nursing); Mr Jon Edwards (data)

- John Hunter Hospital, Newcastle, NSW: Dr Andrew Gill (medical); Ms Susanne Wooderson (nursing); Ms Michelle Giles (data)

- King George V Hospital, Sydney, NSW: Dr Nick Evans (medical); Dr Jane Davey (nursing); Ms Shelley Reid (data)

- Liverpool Hospital, Liverpool, NSW: Dr Robert Guaran (medical); Ms Rebecca Gibson (nursing); Ms Katherine Medlin and Ms Sarah Wilson (data)

- Mater Mothers Hospital, Brisbane, QLD: Dr Peter Gray (medical); Ms Jayne Hegarty (nursing); Mr Andrew Shearman (data)

- Nepean Hospital, Penrith, NSW: Dr Lyn Downe (medical); Ms Ria Koppen (nursing); Ms Mee Fong Chin (data)

- Royal Hospital for Women, Sydney, NSW: Dr Kei Lui (medical) ; Ms Sally Wise (nursing); Ms Diane Cameron (data)

- Royal North Shore Hospital, Sydney, NSW: Dr Jennifer Bowen (medical); Ms Lynnette Grant (nursing); Ms Pamela Hand and Ms Vicky Gallimore (data)

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

Title of Research Project: **A Randomised Trial of Oxygen Therapy on Growth and Development of Infants**

Chief Investigator: **Professor David Henderson-Smart, MB BS, PhD, FRACP Director, Centre for Perinatal Health Se rvices Research University of Sydney, NSW**

PARENTAL CONSENT

I,..…………………..................................... of

....……………….................

....……………….....

Have read and understood the Information for Participants on the above named research study and have discussed the study with

....………………........

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: ....…......................

SIGNATURE: ....……...............

DATE: ....……......

NAME OF WITNESS: …………………………………………………….…

SIGNATURE OF WITNESS: ....……….…

BO⊙ST Trial
2

Benefits Of Oxygen Saturation Targeting Trial

A Randomised Trial of Oxygen Therapy on Growth and Development of Infants

INFORMATION SHEET FOR PARENTS

You are invited to enrol your baby in a study of whether keeping oxygen at a higher level in the blood improves growth and development. The study is being coordinated by the specialist obstetric hospitals in New South Wales. Your baby has been selected as a possible participant in this study because she/he was been born before 30 weeks gestation (premature) and needed extra oxygen for at least 3 weeks after birth.

> Very premature babies commonly need extra oxygen for a long time because of their lung problems , and they o ften do not grow or develop well during the first year of life. There is a standard or usual amount of oxygen in the blood that is kept by monitoring the oxygen saturation (this tells us how much oxygen is in the blood). A certain level is maintained by turning the oxygen higher or lower. You may have heard that in the past very high oxygen given to premature babies caused eye damage, but this level of oxygen is no longer used in modern neonatal intensive care. The amount of oxygen used now is safe, and your baby is considered too old to have any side effects on the eyes from oxygen. We think it is important to find out whether we can improve the health of babies like yours. Doctors are uncertain whether babies will be healthier on lower or higher levels of oxygen, and this is why we are doing this study.

If you agree to participate in this study, your baby will be randomly assigned (like the toss of a coin) to be kept at either the usual or the higher oxygen. Your baby will be kept at either type of oxygen level only for the amount of time that they need extra oxygen. On the one hand, it may take more time for the baby to be weaned off oxygen if they are getting the higher amount, and she/he may be in hospital for a slightly longer time. On the other hand, your baby may go home earlier and not get as many illnesses in the first year, because they are healthier as a result of getting more oxygen. Our study aims to see if overall there is a benefit to babies and their families.

The research nurse will keep track of how much oxygen the baby gets by recording it twice a week. We need to find out how your baby grows and develops, so a research nurse will measure the length, weight, and the size of the head before the baby goes home, and again at one year of age. At the time the baby goes home, again after several months, and at one year, we will also ask you to complete surveys that tell us about how your baby's premature birth affected you. At one year of age, a research psychologist will carry out tests to find out how developed your child is. Because the one year visit involves coming to hospital, we will make an appointment that is convenient for you and give you a refund for the amount it costs to get to hospital.

Title: A Randomised Trial of Oxygen Therapy on Growth and Development of Infants

Any information about you and your baby that we get in this study will remain private and will only be seen by research staff unless any very serious or life threatening problems were uncovered, in which case your baby's doctor would be notified. The results of the study will be published only in a way that will not name you or your baby.

Whether you take part in this study or not, it will not make any difference to the medical care your baby will receive from nurses and doctors in the hospital. If you decide to take part in the study, you can still withdraw at any time and this will not make any difference to your baby's medical care either.

When you have read this information, the research nurse or your doctor will talk to you about the study more and answer any questions you may have. If you have any questions at any time, Professor David Henderson-Smart, or his assistant, Lisa Askie on (02) 9351 7739, or pager: (02) 9963 3540, will be happy to answer them. You will be given a copy of this sheet to keep.

This study has been approved by the Ethics Review Committee of the Central Sydney Area Health Service, which is responsible for King George V Hospital for Mothers and Babies. If you have any worries or complaints about the research study, you can contact the Secretary of the Ethics Review Committee of the Central Sydney Area Health Service on (02) 9515 6766.

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

ENROLMENT FORM

IDENTIFYING DETAILS:

Baby name: _____

Baby record number: |__|__|__|__|__|__|__|__|__|__|__|__|

Date of birth: _____ / _____ / _____
                      day   month   year

Time of birth: _____ : _____

┌─────────────────────────┐
│   │
│   **PATIENT ID STICKER** │
│   │
└─────────────────────────┘

ELIGIBILITY CRITERIA: **Tick box ☑ if applicable**

  Gestational age < 30 weeks

  Oxygen dependent at 32 weeks postmenstrual age

  Parent(s) reside where follow up is possible

Only if all above boxes ticked, then continue: At which perinatal centre is the infant registered:

  John Hunter Hospital   Royal Hospital for Women

  King George V Hospital   Royal North Shore Hospital

  Liverpool Hospital   Mater Mothers Hospital

  Nepean Hospital   Canberra Hospital

EXCLUSION CRITERIA: **Tick box ☑ if applicable**

  Lethal and selected congenital malformations, including: congenital heart defects; congenital lung defects; intestinal atresias or stenoses; anomalies of the abdominal wall. (Please specify):
_____

  Major surgery and disease complications influencing growth and development directly, including: intestinal resections/ostomies/fistulas; ventriculostomies; ventricular shunts. (Please specify):
_____

  Infant expected to die imminently

  Infant not expected to live with the biological mother

  Three or more eligible infants from a multiple confinment

☞ **EXCLUDE INFANT IF ANY OF EXCLUSION CRITERIA ARE TICKED**

Has head ultrasound at approximately 4 weeks of life been performed?   yes   no
If no, then need to wait for ultrasound to be done

If yes, were results: Grade 3 or 4 intraventricular haemorrhage (IVH)

                         Periventricular leukomalacia (PVL)

                         Porencephalic cyst

☞ **EXCLUDE INFANT IF ANY OF BOXES IMMEDIATELY ABOVE ARE TICKED**

☞ **ONLY IF INFANT IS ELIGIBLE, PROCEED TO CONSENT**

CONSENT: Tick box ☑ when completed

First approach to parents by neonatologist or nurse liaison representative

Study explained to parents by neonatologist, nurse liaison representative or research nurse

Consent form signed and witnessed

Parents given a copy of the consent form and information sheet

☞ **IF CONSENT REFUSED OR NOT SOUGHT ON ELIGIBLE INFANTS,**
COMPLETE "REFUSAL / MISSED ELIGIBLES SECTION" NEXT PAGE

☞ **WHEN ALL CONSENT BOXES ARE TICKED, COLLECT RANDOMISATION DETAILS**

RANDOMISATION DETAILS:

Perinatal Centre No.: |__|__|__|__|

Confinement Status: Singleton   Unrelated Multiple   Related Multiple

Gestational Age Grouping: 23-27 weeks   28-29 weeks

Primary doctor: _____

Dr's phone number: (   ) _____

☞ **WHEN ALL ABOVE DETAILS ARE COMPLETE, PROCEED TO RANDOMISATION**

Contact: Study Coordinator on (02) 9351 7739 or call: 016-020 & ask for pager no. 225 656

Eligibility will be counter-checked and Study Coordinator will organise randomisation.

☞ **ONCE COMPLETE, PLACE THIS FORM IN BOOST PROCEDURE MANUAL IN**
"COMPLETED ENROLMENT FORMS" SECTION - Study Coordinator will collect

To be completed by Study Coordinator:

Study Identifier No.: |__|__|__|__|__| – |__|__|__|__|

Date of randomisation: _____/_____/_____
                                          day   month   year

Date study intervention commenced: _____ / _____ / _____
                                                               day   month   year

NICUS number: |__|__|__|__|__|__|__| (if applicable)

Research nurse initials: _____   Study coordinator initials: _____

2

BO❂ST Trial
2
Benefits Of Oxygen Saturation Targeting Trial

REFUSALS / MISSED ELIGIBLES SECTION: Complete this section only if applicable

IDENTIFYING DETAILS:

Baby name: _____

Baby record number: | | | | | | | | | | | | |

Date of birth: _____ / _____ / _____
                              day   month   year

Registration hospital: _____

NICUS number: | | | | | | | | |

	PATIENT ID STICKER

Reason for refusal: parent(s) refused (baby believed to be too ill)

(by parents)   parent(s) refused (protection of baby)

                                       parent(s) refused (other)
                                       please specify _____

Reason for missed eligible: doctor refused (baby believed to be too ill)

(eligible but not asked)   doctor refused (protection of parents)

                                        doctor refused (other)
                                        please specify _____

                                        assessed too late for inclusion

                                        unknown

                                        other
                                        please specify _____

ONCE COMPLETE, PLACE THIS FORM IN BOOST PROCEDURE MANUAL IN

"COMPLETED ENROLMENT FORMS" SECTION - Study Coordinator will collect

3

Sample BOOST trial promotional material

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

OXYGEN / NURSING DEPENDENCY / WEIGHT FORM (Clinical Data Form 2)

Study Identifier No.: ⌊ ⌊ ⌊ ⌊ – ⌊ ⌊ ⌊   **Baby's name:** _____

	from notes:		*from download:*			*from notes:*	
Date	**FiO₂(%/lpm) Range**	**/ SpO₂ (median) (middle value)**	**SpO₂ (median)**	**SpO₂ (mode)**	**% time spent in target range**	**Dependency level**	**Weight**
_____	_____ / _____		_____	_____	_____ %	_____	_____ g
_____	_____ / _____		_____	_____	_____ %	_____	_____ g
_____	_____ / _____		_____	_____	_____ %	_____	_____ g
_____	_____ / _____		_____	_____	_____ %	_____	_____ g
_____	_____ / _____		_____	_____	_____ %	_____	_____ g
_____	_____ / _____		_____	_____	_____ %	_____	_____ g

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

CLINICAL DATA FORM (Data form 1)

IDENTIFYING DETAILS:

Study Identifier No.: |⎽|⎽|⎽|⎽|⎽| – |⎽|⎽|⎽|⎽|

Download files name: _____

Baby surname: _____ Baby first name: _____

Also known as: surname _____ first name _____

Baby medical record number: |⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|

Baby date of birth: _____/_____/_____ Time of birth: _____ : _____
day month year

Hospital/place of delivery: _____

Perinatal Centre for trial enrolment:

☐ Canberra Hospital ☐ Nepean Hospital
☐ John Hunter Hospital ☐ Royal Hospital for Women
☐ King George V Hospital ☐ Royal North Shore Hospital
☐ Liverpool Hospital ☐ Mater Mothers Hospital

NICUS number: |⎽|⎽|⎽|⎽|⎽|⎽|⎽| Transferred via NETS: ☐ yes ☐ no

CLINICAL DATA FOR BABY:

Gestational age: |⎽|⎽|⎽| weeks

Sex: ☐ Unknown ☐ Male ☐ Female ☐ Ambiguous

Plurality: ☐ Singleton ☐ Twins ☐ Triplets ☐ Quads ☐ More

Birth order: ☐ Singleton ☐ First ☐ Second ☐ Third ☐ Fourth

Study ID No. |⎽|⎽|⎽|⎽|⎽| – |⎽|⎽|⎽|⎽|

1

Birthweight: ⊥⊥⊥⊥⊥ grams

Head circumference at birth: ⊥⊥⊥ . ⊥⊥ centimetres

Length at birth (or first attended): ⊥⊥⊥ . ⊥⊥ cm _____/_____/_____
         and date attended   day   month   year

1 minute Apgar score: ⊥⊥⊥   5 minute Apgar score: ⊥⊥⊥

Primary respiratory diagnosis:
- ☐ Unknown
- ☐ Hyaline membrane disease
- ☐ Pneumonia
- ☐ Immature lung
- ☐ Congenital anomaly
- ☐ Transient tachypnoea of newborn
- ☐ Meconium aspiration
- ☐ Pulmonary hypertension
- ☐ Apnoea
- ☐ Other (specify)_____

Surfactant: yes   no

Patent ductus arteriosus: yes   no

    If yes, treatment with: Indomethacin   Surgery

                       Other (specify)_____

Apnoea/bradycardia requiring treatment: yes   no

    If yes, type of treatment: Methylxanthines   CPAP

                       Other (specify)_____

Total days TPN: ⊥⊥⊥⊥⊥ days

Postnatal steroids for lung disease: yes   no

Abnormal CLD CXR & O_2 dependent at 36 weeks pma: yes   no

Diuretic therapy for chronic lung disease: yes   no

Worst episode of necrotising enterocolitis:

    None   Clinical diagnosis   Proven radiologically/at surgery

Worst grade of IVH:

    None   Grade I   Grade II   Grade III   Grade IV

Study ID No. ⊥⊥⊥⊥⊥⊥ – ⊥⊥⊥⊥

Worst grade of ROP: *Right eye*

      Normal   Grade I   Grade II   Grade III   Grade IV

Worst grade of ROP: *Left eye*

      Normal   Grade I   Grade II   Grade III   Grade IV

Treatment for ROP: yes   no

If Yes, was treatment: one eye   both eyes

OXYGEN CONSUMPTION:

A. <u>General:</u>   Date supplemental oxygen started: _____/_____/_____
                                                       day   month   year

                Date supplemental oxygen last needed: _____/_____/_____
                                                        day   month   year

Total days in oxygen (all types of administration): |__|__|__|__| days

B. <u>Was infant ever ventilated?:</u>   yes   no   *If yes* :

Date assisted ventilation (mechanical vent or CPAP) started: _____/_____/_____
                                                                   day   month   year

Date assisted ventilation (mechanical vent +all CPAP) completed: _____/_____/_____
                                                                      day   month   year

Total days of mechanical ventilation (IMV, IPPV, HFV, SIMV, SIPPV): |__|__|__|__| days

Total days of CPAP (continuous via ETT, NP, nasal prongs): |__|__|__|__| days

Total days of CPAP (intermittent via NP, nasal prongs): |__|__|__|__| days

Total days of assisted ventilation (mechanical ventilation + all CPAP): |__|__|__|__| days

Treated with high frequency ventilation: yes   no

Was home oxygen required?:   yes   no   *If yes*:

Date commenced home oxygen: _____ / _____ / _____
                                                    day   month   year

Date completed home oxygen: _____ / _____ / _____
                                                    day   month   year

Total days of home oxygen: └─┴─┴─┴─┘ days

ENROLMENT IN OTHER STUDIES:

Enrolled in Oracle trial: yes   no

Enrolled in ActoMgSO$_4$ trial: yes   no

Enrolled in TIPP trial: yes   no

Enrolled in any other trial: yes   no

                              If yes, specify: _____

_____

PHYSICAL MEASUREMENTS AT 38 WEEKS POSTMENSTRUAL AGE (pma):

Weight at 38 weeks pma: └─┴─┴─┴─┴─┘ grams   Date:_____ / _____ / _____
                                                            day   month   year

Length at 38 weeks pma: └─┴─┘ . └─┴─┘ cm   Date:_____ / _____ / _____
                                                            day   month   year

Head circ at 38 weeks pma: └─┴─┘ . └─┴─┘ cm   Date:_____ / _____ / _____
                                                            day   month   year

Grade 3 or 4 ROP (any eye) at 38 weeks pma: yes   no

Death by 38 weeks pma: yes   no

Study ID No. └─┴─┴─┴─┴─┘ – └─┴─┴─┴─┘

4

FEEDING AND NUTRITION DATA:

Date established all sucking feeds: _____ / _____ / _____
day month year

Date birthweight regained and maintained: _____ / _____ / _____
day month year

Feeding at discharge to home:

fully breast fed   combination breast/formula fed   formula fed

TRANSFER/DISCHARGE DATA:

During hospitalisation, was the baby **transferred temporarily** :   yes   no

If yes, was the baby transferred to: another Level 3 NICU

a Level 4 NICU

other (specify) _____

Discharged from registration hospital on: _____/_____/_____
day month year

From the registration hospital,

was the baby **discharged** to: home

another Level 3 NICU

specify hospital _____

specify reason _____

_____

level 4 NICU

specify hospital _____

specify reason _____

_____

level 2 nursery

specify hospital_____

specify reason _____

_____

Study ID No. |__|__|__|__|__| – |__|__|__|__|

other hospital/setting (e.g. interstate, overseas, fostered)

specify setting _____

specify reason _____

_____

Date of **final discharge** from all hospitals: _____/_____/_____
day   month   year

Total days of initial hospitalisation: |___|___|___|___| days

STUDY INTERVENTION DETAILS:

Commencement of study intervention:

Randomisation Status: Singleton   Unrelated Multiple   Related Multiple

Gestational Age Grouping: 24-27 weeks   28-29 weeks

Date reached 32 weeks pma: _____ / _____ / _____
day   month   year

Date of randomisation: _____/_____/_____
day   month   year

Date study intervention commenced: _____ / _____ / _____
day   month   year

Age at randomisation (*in pma weeks + days eg 32+3 wks*): _____ weeks

Completion of study intervention:

Date study intervention (supplemental O2) ceased: _____ / _____ / _____
day   month   year

Download in air after one week off study intervention: Normal   Abnormal

Date study oximeter removed (final):   _____ / _____ / _____
day   month   year

Study ID No. |___|___|___|___|___| - |___|___|___|___|

<u>Temporary removal from study intervention:</u>(*complete only if applicable)*

Date removed   Date returned   Reason for removal   Authorised by

___ / ___ / ___   ___ / ___ / ___   _____   _____

___ / ___ / ___   ___ / ___ / ___   _____   _____

NURSING DEPENDENCY DATA: During initial hospitalisation:

Total days at Level 4   dependency: |__|__|__|__| days

Total days at Level 3   dependency: |__|__|__|__| days

Total days at Level 2a   dependency: |__|__|__|__| days

Total days at Level 2b   dependency: |__|__|__|__| days

CLINICAL DATA FOR MOTHER:

Mother's age: |__|__|__| years   Mother's height: |__|__|__|__| cm

Total no. previous pregnancies: |__|__|__| Total no. deliveries $\geq$20wks &/or BW $\geq$ 400g |__|__|__|

Previous preterm birth ($\geq$ 20wks &/or BW $\geq$ 400g)   Yes   No

Total no. previous perinatal deaths ($\geq$20wks &/or BW $\geq$400g & died $\leq$ 28 days) |__|__|__|

Antenatal steroids: Unknown   None   < 24 hours   Complete   >7 days

Delivery:

  Normal vaginal   Forceps   Forceps rotation   Vacuum extraction

  Vaginal breech   CS not in labour (elective)   CS in labour (emergency)

Study ID No. |__|__|__|__|__| – |__|__|__|__|

7

SOCIAL/OTHER DATA FOR MOTHER:

Marital status: Married/de facto   Single   Divorced/widowed

Insurance status: Medicare   Private

Mother's country of birth: _____

Mother's ethnic/racial origin:

       Unknown   Caucasian

       Aboriginal/Torres Strait Islander   Asian

       Other (describe) _____

Primary language spoken at home by mother: _____

Highest level of mother's education completed:

   Some primary school   Completed HSC

   Primary school   Some trade, TAFE or university

   Some secondary school   Completed trade or TAFE

   Completed school certificate   Completed university

Prior to the baby's birth was the mother working in paid employment: yes   no

    If yes: Part-time   Full-time

Mother's current occupation: _____

Mother's usual occupation: _____

Financial support received (tick all that apply):

       Single parent pension   Invalid pension

       Unemployment benefit   Child disability allowance

       Other benefit (specify) _____

SOCIAL/OTHER DATA FOR FATHER:

Father's age: ⌊⌊⌊⌋ years   Father's height: ⌊⌊⌊⌊⌋ cm

Father's country of birth: _____

Father's ethnic/racial origin:

      Unknown   Caucasian

      Aboriginal/Torres Strait Islander   Asian

      Other (describe) _____

Primary language spoken at home by father: _____

Highest level of father's education completed:

  Some primary school   Completed HSC

  Primary school   Some trade, TAFE or university

  Some secondary school   Completed trade or TAFE

  Completed school certificate   Completed university

Is father currently employed: yes   no

    If yes: Part-time   Full-time

Father's current occupation: _____ __

Father's usual occupation: _____

Financial support received (tick all that apply)

     Unemployment benefit

     Invalid pension

     Other benefit (specify) _____

Study ID No. ⌊⌊⌊⌊⌊⌋ – ⌊⌊⌊⌊⌋

CONTACT DETAILS:

Mother:

Mother's surname: _____ Mother's first name: _____

Mother's address:_____ (Street)

_____ (Suburb/City/Town)

Mother's phone: (_____)_____

Father:

Father's surname: _____ Father's first name: _____

Father's address: _____(Street)
(if different from mother's)

_____ (Suburb/City/Town)

Father's phone: (_____)_____
(if different from mother's)

Grandmother (mother's mother):

Surname: _____ First name: _____

Address: _____ (Street)

_____ (Suburb/City/Town)

Phone: (_____)_____

Other:

If the maternal grandmother is unavailable, have parent(s) nominate one other person who is likely to know their whereabouts beyond the coming year.

Other relation to parent(s): _____

Other surname: _____ Other first name: _____

Other address: _____ (Street)

_____ (Suburb/City/Town)

Other phone: (_____)_____

Study ID No. └─┴─┴─┴─┴─┘ - └─┴─┴─┴─┘

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

4 MONTHS CORRECTED FOLLOW-UP FORM (Data form 6)

IDENTIFYING DETAILS:

Study Identifier No.:   .: |_|_|_|_|_| - |_|_|_|_|

Baby surname: _____   Baby first name: _____

Also known as: surname _____   first name _____

Date of birth: _____/_____/_____
                    day   month   year

Baby medical record number: |_|_|_|_|_|_|_|_|_|_|_|_|

Perinatal Centre for trial registration:

   John Hunter Hospital   Royal Hospital for Women

   King George V Hospital   Royal North Shore Hospital

   Liverpool Hospital   Mater Mothers' Hospital

   Nepean Hospital   The Canberra Hospital

CLINICAL DATA AT 4 MONTHS CORRECTED AGE:

Date reached 4 months corrected: _____/_____/_____
                                        day   month   year

Weight: |_|_|_|_|_| grams   Date:_____ / _____ / _____
                                              day   month   year

Head circ: |_|_| . |_|_| centimetres   Date:_____ / _____ / _____
                                              day   month   year

Length: |_|_| . |_|_| centimetres   Date:_____ / _____ / _____
                                              day   month   year

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

12 MONTHS CORRECTED FOLLOW-UP FORM (Data form 7)

*IDENTIFYING DETAILS***:**

Study Identifier No.: |⎽|⎽|⎽|⎽|⎽| **-** |⎽|⎽|⎽|⎽|

Baby surname: _____ Baby first name: _____

Also known as: surname _____ first name _____

Date of birth: _____/_____/_____   NICUS No. |⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|
  day month year

Baby medical record number: |⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|

Date reached 12 months corrected age: _____/_____/_____
  day month year

☐ Griffiths ☐ Eyes ☐ Hearing

*1. PHYSICAL / NEUROLOGICAL EXAMINATION***:**

Date of physical/neuro assessment: _____/_____/_____
  day month year

Physical/neuro assessment was completed at:

☐ Canberra Hospital ☐ Nepean Hospital
☐ John Hunter Hospital ☐ Royal Hospital for Women
☐ King George V Hospital ☐ Royal North Shore Hospital
☐ Liverpool Hospital ☐ Mater Mothers Hospital
☐ Other - please specify: _____

SID : |⎽|⎽|⎽|⎽|⎽| - |⎽|⎽|⎽|⎽|

1

PHYSICAL EXAMINATION

Growth Parameters

Weight ....… kgs

Height .... cms

Head Circumference .... cms

Physical Examination Normal / Abnormal If "Abnormal", please specify:-

....

....

....

....

NEUROLOGICAL PROBLEMS **Newly diagnosed since discharge:** Y / N

Meningitis / Encephalitis Y / N / Unknown

    If yes, are there any sequelae? Y / N

    If yes, please specify:-

Hydrocephalus Y / N / Unknown

    If yes: Age diagnosed .... months

            Type Congenital / Acquired

            Treatment Shunt / Reservoir / Arrested

Seizures Y / N / Unknown

    If yes: Age of onset .... months

            Type(s) Febrile / Partial / Generalised / Syndrome (specify)

            No. in the last year: 0 / 1 or more

Other Neurological Problems Y / N / Unknown

        Porencephalic cyst Y / N

        Cortical atrophy Y / N

        Periventricular leucomalacia Y / N

SID : |_|_|_|_|_| - |_|_|_|_|

Summary of Neurological Checklist :

    1 = NORMAL

    2 = PROVISIONAL DIAGNOSIS OF CEREBRAL PALSY / MOTOR DELAY WITH
          NEUROLOGICAL SIGNS

    3 = MOTOR DELAY, WITH OR WITHOUT SUSPECT NEUROLOGICAL SIGNS

    If "2" circled, i.e. provisional diagnosis of cerebral palsy, then: -

        Severe functional disability due to cerebral palsy   Yes / No

        (where "Severe functional disability" = not sitting independently)

Oro-motor function

Problems : -   Treatment:-

Chewing	Y / N		Tube Feeding	Y / N
Drooling	Y / N	Gastrostomy	Y / N	
Swallowing	Y / N	Speech Therapy	Y / N	
Voice	Y / N	Other	Y / N	

                                      If yes, please specify:-

THERAPEUTIC SERVICES USED

Have any of the following services or treatment been used for this child since discharge?

                                    Past, but not current / **N**o / **R**eferred / **C**urrent

Hearing Impairment Centre	P / N / R / C
Visual Impairment Centre	P / N / R / C
Motor Impairment Centre	P / N / R / C
Developmental Disability Centre	P / N / R / C
Emotional / Behavioural problem advice	P / N / R / C
Physiotherapy	P / N / R / C
Occupational therapy	P / N / R / C
Speech pathology	P / N / R / C
Other early intervention	P / N / R / C
Dept of Community Services (DOCS)	P / N / R / C

SID : |_|_|_|_|_| - |_|_|_|_|

2. HEARING TEST

Date of Most Recent Test .... **Who Tested** ....

TYPE OF TEST

RESULTS	BAER	NOISEMAKERS	VROA	AUDIO GRAM	TYMPANO GRAM	OTO ACOUSTIC EMISSION
Normal (L)	Y / N			Y / N	Y / N	Pass / Fail
Normal (R)	Y / N			Y / N	Y / N	Pass / Fail
Passed 30dB screen			Y / N			
Severe loss excluded		Y / N				

RESULT Normal / Abnormal / Ongoing surveillance / Unknown

If Abnormal:- **R**ight / **L**eft / **B**oth

Conductive deafness R / L / B
Sensory Neural deafness R / L / B
High Frequency Loss Y / N

If deafness present,

Level of loss in *better* ear:- mild (30-40 dB) Y / N
moderate (41-60 dB) Y / N
severe (61-90 dB) Y / N
profound ($\geq$91 dB) Y / N

HEARING AID in place R / L / B VENTILATION TUBES in place R / L / B / Nil

3. VISION TEST

Date of Most Recent Test .... **Who tested** ....

RESULT Normal / Abnormal / Ongoing Surveillance / Unknown

If abnormal:- **N**one / **R**ight / **L**eft / **B**oth

Myopia	N / R / L / B	Strabismus	N / R / L / B
Retinopathy	N / R / L / B	Tortuosity of retinal vessels	N / R / L / B
Surgery	N / R / L / B	Patching	N / R / L / B
Corrective Lenses	N / R / L / B	Drops	N / R / L / B
Blind	N / R / L / B		

SID : |___|___|___|___|___| - |___|___|___|___|

4. DEVELOPMENT

Type of developmental assessment test: Revised Griffiths / "Old" Griffiths / Unknown / Other (specify)

....

Date of Assessment ....

Name of Person Administering Test ....

Address ....

....

RESULTS OF REVISED GRIFFITHS SCORE

Scale	Raw Score	Age Equivalent score(mths)	Sub and General Quotients	Percentile Score
A Locomotor				
B Personal-Social				
C Hearing-Language				
D Hand-Eye				
E Performance				
TOTAL				

<u>Any Other Problems?</u>

If yes, please specify:-

CHECKLISTS

Have the following been received, completed and returned ?

1) Toddler Temperament completed   Y / N

2) Parenting Stress Index completed   Y / N

3) Impact on Family Scale completed   Y / N

4) Edinburgh Postnatal Depression Scale completed   Y / N

SID : |__|__|__|__|__| - |__|__|__|__|

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

DEATH REGISTRATION FORM (Data Form 5)

IDENTIFYING DETAILS:

Study Identifier No.: |__|__|__|__|__| – |__|__|__|

Baby surname: _____ Baby first name: _____

Baby medical record number: |__|__|__|__|__|__|__|__|__|__|__|

Baby date of birth: _____/_____/_____
                              day   month   year

DETAILS OF DEATH:

Baby date of death: _____/_____/_____
                            day   month   year

Place of death: Hospital: (specify): _____

                     Home

                     Other: (specify): _____

Primary cause of death: _____

ICD-9 code: |__|__|__|__| . |__|__|__|

Source of data: Hospital discharge summary

                  Autopsy/postmortem

                  Death certificate

                  Coroner's report

                  Other (specify)_____

Primary doctor: _____

Dr's phone number (   ) _____

Research nurse initials _____

SID : |__|__|__|__|__|__| - |__|__|__|__|

Retinopathy of prematurity (ROP) screening report form

TABLE. Retinopathy of Prematurity (ROP) Ophthalmic Examination Record*

BIOGRAPHICAL DATA

Name_____   Hospital # __ __ __ __ __ __ __

Birthdate (MM/DD/YY) __ __ / __ __ / __ __   Sex (M=1, F=2) __

Birthweight (grams) __ __ __ __   Gestational Age (weeks) __ __

Multiple Births (Single=1, Twin=2, Triplet=3) __

EXAMINATION

Date of Exam __ __ / __ __ / __ __   Examiner's Initials or # __ __ __

— CLOCK HOURS —

MACULA   OPTIC N.   ORA SERRATA   RE   LE
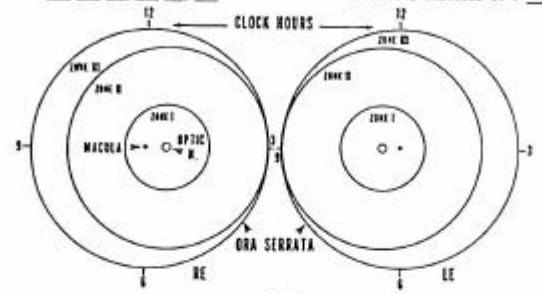
ZONE
Mark with 'X'

Z 1   Z 2   Z 3   Z 1   Z 2   Z 3

STAGE AT CLOCK HOURS

Blank=normal
1=Demarcation line
2=Ridge
3=2+Extraret prolif
4=3+Retinal detach
9=No information

Mark highest stage at every clock hour

If Stage 3: 1=mild, 2=moderate, 3=severe

If Stage 4: 1=exudative, 2=tractional, 3=combined

Other Findings
Mark with 'X'

O.D.   O.S.

A Dilatation/tortuosity posterior vessels
B Iris vessel dilatation
C Pupil rigidity
D Vitreous haze
E Hemorrhages

Cicatricial RLF (Reese, 1953)
Mark with 'X'

O.D.   O.S.

I.   Small mass opaque tissue in periphery without detachment
II.   Larger mass opaque tissue in periphery with localized detachment
III. Larger mass in periphery with traction fold to disc
IV.   Retrolental tissue covering part of pupil
V.   Retrolental tissue covering entire pupillary area

COMMENTS:

Signature

* Format permits complete recording of detailed examination results both graphically employing retinal drawing and numerically for later analysis if desired.

EDINBURGH POSTNATAL DEPRESSION SCALE

Stage: ☐ Entry   ☐ 38 weeks pma   ☐ 4 months   ☐ 12 months

As you have recently had a baby, we would like to know how you are feeling. Please UNDERLINE the answer which comes closest to how you have felt PAST SEVEN DAYS,
not just how you feel today.

Here is an example, already completed.

I have felt happy:
    Yes, all the time.
    <u>Yes most of the time.</u>
    No, not very often.
    No, not at all.

This would mean :"I have felt happy most of the time" during the past week.
Please complete the other questions in the same way.

IN THE PAST SEVEN DAYS:

1. I have been able to laugh and see the funny side of things
    1 As much as I always could
    2 Not quite so much now
    3 Definitely not so much now
    4 Not at all

2. I have looked forward with enjoyment to things
    1 As much as I ever did
    2 Rather less than I used to
    3 Definitely less than I used to
    4 Hardly at all

3. I have blamed myself unnecessarily when things went wrong
    1 Yes, most of the time
    2 Yes, some of the time
    3 Not very often
    4 No, never

4. I have been anxious and worried for no good reason
    1 No, not at all
    2 Hardly ever
    3 Yes, sometimes
    4 Yes, very often

SID: ⌊⌊⌊⌊⌊ - ⌊⌊⌊⌊⌊

5. I have felt scared or panicky for no good reason
      1 Yes, quite a lot
      2 Yes, sometimes
      3 No, not much
      4 No, not at all

6. Things have been getting on top of me
      1 Yes, most of the time I haven't been able to cope
      2 Yes, sometimes I haven't been able to cope as well as usual
      3 No, most of the time I have coped well
      4 No, I have been coping as well as ever

7. I have been so unhappy that I have had difficulty sleeping
      1 Yes, most of the time
      2 Yes, sometimes
      3 Not very often
      4 No, not at all

8. I have felt sad or miserable
      1 Yes, most of the time
      2 Yes, quite often
      3 Not very often
      4 No, not at all

9. I have been so unhappy that I have been crying
      1 Yes, most of the time
      2 Yes, quite often
      3 Only occasionally
      4 No, never

10. The thought of harming myself has occurred to me
      1 Yes, quite often
      2 Sometimes
      3 Hardly ever
      4 Never

SID: ⊥⊥⊥⊥⊥ - ⊥⊥⊥⊥⊥

SHORT TEMPERAMENT SCALE FOR INFANTS (4-8 MONTHS OF AGE) *

FOR EACH QUESTION, PLEASE CIRCLE THE NUMBER WHICH BEST DESCRIBES YOUR CHILD'S RECENT AND CURRENT BEHAVIOUR.

IF ANY QUESTION DOES NOT APPLY TO YOUR CHILD OR CANNOT BE ANSWERED, JUST DRAW A LINE THROUGH IT.

* Copyright ATP 1987

Study ID No. |__|__|__|__| - |__|__|__|

	Almost never	Not often	Variable, usually does not	Variable, usually does	Frequently	Almost always
1. The baby is fretful on waking up and/or going to sleep (frowns, cries).	1	2	3	4	5	6
2. The baby accepts straight away any change in place or position of feeding, or person giving the feed.	1	2	3	4	5	6
3. The baby is shy (turns away or clings to mother) on meeting another child for the first time.	1	2	3	4	5	6
4. The baby continues to fret during nappy change in spite of efforts to distract him/her with game, toy or singing etc.	1	2	3	4	5	6
5. The baby amuses self for 1/2 hour or more in cot or playpen (looking at mobile, playing with toy, etc.)	1	2	3	4	5	6
6. The baby moves about a lot (kicks, grabs squirms) during nappy-changing and dressing.	1	2	3	4	5	6
7. The baby makes happy sounds (coos, smiles, laughs) when being changed ore dressed.	1	2	3	4	5	6
8. The baby is pleasant (smiles, laughs) when first arriving in unfamiliar places (friend's house, shop).	1	2	3	4	5	6
9. The baby gets sleepy at about the same time each evening (within 1/2 hour).	1	2	3	4	5	6
10. The baby accepts regular procedures (hair brushing, face washing, etc) at any time without protest.	1	2	3	4	5	6
11. The baby moves a lot (squirms, bounces, kicks) while lying awake in cot.	1	2	3	4	5	6
12. For the first few minutes in a new place or situation (new shop or home) the baby is fretful.	1	2	3	4	5	6
13. The baby continues to cry in spite of several minutes of soothing.	1	2	3	4	5	6
14. The baby keeps trying to get a desired toy, which is out of reach, for 2 minutes or more.	1	2	3	4	5	6
15. The baby greets a new toy with a loud voice and much expression of feeling (whether positive or negative).	1	2	3	4	5	6

Study ID No. ⌊⌊⌊⌊⌋ -⌊⌊⌊⌋

	Almost never	Not often	Variable, usually does not	Variable, usually does	Frequently	Almost always
16. The baby's first reaction (at home) to approach by strangers is acceptance.	1	2	3	4	5	6
17. The baby wants daytime naps at differing times (over 1 hour difference) from day to day.	1	2	3	4	5	6
18. The baby cries when left to play alone.	1	2	3	4	5	6
19. The baby's daytime naps are about the same length from day to day (less than 1/2 hour difference).	1	2	3	4	5	6
20. The baby displays much feeling (strong laugh or cry) during changing or dressing.	1	2	3	4	5	6
21. The baby wants and takes feedings at about the same time (with 1 hour) from day to day.	1	2	3	4	5	6
22. The baby is content (smiles, coos) during interruptions of milk or solid feeds.	1	2	3	4	5	6
23. The baby accepts within a few minutes a change in place of bath or person giving the bath.	1	2	3	4	5	6
24 The baby's time of waking in the morning varies greatly (by 1 hour or more) from day to day.	1	2	3	4	5	6
25. The baby reacts strongly to strangers; laughing or crying.	1	2	3	4	5	6
26. The baby's period of greatest activity comes at the same time of day.	1	2	3	4	5	6
27. The baby is irritable or moody throughout a cold or a stomach virus.	1	2	3	4	5	6
28. The baby can be distracted from fretting or squirming during a procedure (nail cutting, hair brushing, etc) by a game, singing, TV, etc.	1	2	3	4	5	6
29. The baby's first reaction to seeing doctor or infant welfare sister is acceptance (smiles, coos).	1	2	3	4	5	6
30. The baby lies still during procedures like hair brushing or nail cutting	1	2	3	4	5	6

Study ID No. ⌊⌊⌊⌊⌋ -⌊⌊⌊⌋

SHORT TEMPERAMENT SCALE FOR TODDLERS*

12 months corrected

FOR EACH QUESTION, PLEASE CIRCLE THE NUMBER WHICH BEST DESCRIBES YOUR CHILD'S <u>RECENT</u> AND <u>CURRENT BEHAVIOUR</u>.

IF ANY QUESTION DOES NOT APPLY TO YOUR CHILD OR CANNOT BE ANSWERED, JUST DRAW A LINE THROUGH IT.

* The STST is an uncopyrighted abbreviation of The Toddler Temperament Scale (Fullard, McDevitt
&
Carey 1978) The original TTS is copyrighted in the U S

Study ID No. ⌊⌊⌊⌊⌋ -⌊⌊⌊⌋

	Almost never	Not often	Variable, usually does not	Variable, usually does	Frequently	Almost always
1. The child gets sleepy at about the same time each evening (within 1/2 hour).	1	2	3	4	5	6
2. The child is pleasant (smiles, laughs), when first arriving in unfamiliar places.	1	2	3	4	5	6
3. The child plays continuously for more than 10 minutes at a time with a favourite toy.	1	2	3	4	5	6
4. The child sits still while waiting for food.	1	2	3	4	5	6
5. The child cries after a fall or bump.	1	2	3	4	5	6
6. The child fusses or whines when bottom is cleaned after bowel movements.	1	2	3	4	5	6
7. The child smiles when unfamiliar adults play with him/her.	1	2	3	4	5	6
8. The child responds to frustration intensely (screams, yells).	1	2	3	4	5	6
9. The child eats about the same amount of solid food at meals from day to day.	1	2	3	4	5	6
10. The child remains pleasant when hungry and waiting for food to be prepared.	1	2	3	4	5	6
11. The child allows face washing without protest (squirming, turning away).	1	2	3	4	5	6
12. The child plays actively (bangs. throws runs) with toys indoors.	1	2	3	4	5	6
13. The child ignores voices when playing with a favourite toy.	1	2	3	4	5	6
14. The child wants a snack at a different time each day (over one hour difference).	1	2	3	4	5	6
15. The child runs to get where he/she wants to go.	1	2	3	4	5	6
16. The child takes daytime naps at differing times (over 1/2 hour difference) each day.	1	2	3	4	5	6
17. The child is outgoing with adult strangers outside the home	1	2	3	4	5	6
18. The child stops play and watches when someone walks by.	1	2	3	4	5	6

Study ID No. |__|__|__|__| - |__|__|__|

	Almost never	Not often	Variable, usually does not	Variable, usually does	Frequently	Almost always
19. The child goes back to the same activity after brief interruption (snack, trip to toilet).	1	2	3	4	5	6
20. The child continues to play with a toy in spite of sudden noises from outdoors (car horn, siren etc).	1	2	3	4	5	6
21. The child has moody "off" days when he/she is irritable all day.	1	2	3	4	5	6
22. The child stays with a routine task (dressing, picking up toys) for 5 minutes or more.	1	2	3	4	5	6
23. The child stops eating and looks when he/she hears a sudden noise (telephone, doorbell).	1	2	3	4	5	6
24. The child sits still (moves little) during procedures like hair brushing or nail cutting.	1	2	3	4	5	6
25. The child shows much bodily movement (stomps, writhes, swings arms) when upset or crying.	1	2	3	4	5	6
26. The child's initial reaction at home to approach by strangers is acceptance (looks at, reaches out).	1	2	3	4	5	6
27. The child stops to examine new objects thoroughly (5 minutes or more).	1	2	3	4	5	6
28. The child is moody for more than a few minutes when corrected or disciplined.	1	2	3	4	5	6
29. The child is still shy of strangers after 15 minutes.	1	2	3	4	5	6
30. The child frowns or complains when left to play by self.	1	2	3	4	5	6

IMPACT ON FAMILY SCALE

The following statements have been made by people living with a child who is, or has been, ill. **Please circle** the number which best reflects whether you strongly agree, agree, disagree or strongly disagree with each statement *at the present time*.

Statements that include "my child's illness" or "my child's state" are referring to your child's prematurity, neonatal intensive care stay, and need for ongoing follow-up. Please try to answer honestly. Your answers are anonymous and will help us get a better idea of how having a premature baby affects families as a whole.

	Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**
1. The illness is causing financial problems for the family	1	2	3	4
2. I worry about what will happen to my child in the future (when he/she grows up, when I am not around)	1	2	3	4
3. Relatives interfere and think they know what's best for my child	1	2	3	4
4. Additional income is needed in order to cover medical expenses	1	2	3	4
5. Because of the illness, we are not able to travel out of the city	1	2	3	4
6. People in the neighbourhood treat us specially because of my child's illness	1	2	3	4
7. We have little desire to go out because of my child's illness	1	2	3	4
8. It is hard to find a reliable person to take care of my child	1	2	3	4
9. Sometimes we have to change plans about going out at the last minute because of my child's state	1	2	3	4
10. We see family and friends less because of the illness	1	2	3	4

	Strongly Agree	Agree	Disagree	Strongly Disagree
11. Because of what we have shared we are a closer family	1	2	3	4
12. Sometimes I wonder whether my child should be treated "specially" or the same as a normal child	1	2	3	4
13. My relatives have been understanding and helpful with my child	1	2	3	4
14. I think about not having more children because of the illness	1	2	3	4
15. My partner and I discuss my child's problems together	1	2	3	4
16. We try to treat my child as if he/she were a normal child	1	2	3	4
17. I don't have much time left over for other family members after caring for my child	1	2	3	4
18. Our family gives up things because of my child's illness	1	2	3	4
19. Fatigue is a problem for me because of my child's illness	1	2	3	4
20. I live from day to day and don't plan for the future	1	2	3	4
21. Nobody understands the burden I carry	1	2	3	4
22. Travelling to the hospital is a strain on me	1	2	3	4
23. Learning to manage my child's illness has made me feel better about myself	1	2	3	4
24. Sometimes I feel like we live on a roller coaster: in crisis when my child is acutely ill, OK when things are stable	1	2	3	4

If you have *other children in your household*, please respond to the following statements.

	Strongly Agree	Agree	Disagree	Strongly Disagree
25. It is hard to give much attention to the other children because of the needs of my child	1	2	3	4
26. Having a child with an illness makes me worry about my other children's health	1	2	3	4

If the *other children in your household are 4 years or older*, please respond to the following statements:

	Strongly Agree	Agree	Disagree	Strongly Disagree
27. There is fighting between the children because of my child's special needs	1	2	3	4
28. My other children are frightened by my child's illness	1	2	3	4
29. My other children seem to have more illnesses, aches and pains than most children their age	1	2	3	4
30. The school grades of my other children suffer because of my child's illness	1	2	3	4

PSI   Short Form

Instructions

This questionnaire contains 36 statements. Read each statement carefully. For each statement, please focus on the child you are most concerned about, and circle the response that best represents your opinion.

Circle the SA if you <u>strongly agree</u> with the statement.

Circle the A if you <u>agree</u> with the statement.

Circle the NS if you are <u>not sure</u>.

Circle the D if you <u>disagree</u> with the statement.

Circle the SD if you <u>strongly disagree</u> with the statement.

For example, if you sometimes enjoy going to the movies, you would circle A in response to the following statement:

I enjoy going to the movies.   SA   A   NS   D   SD

While you may not find a response that exactly states your feelings, please circle the response that comes closest to describing how you feel. YOUR FIRST REACTION TO EACH QUESTION SHOULD BE YOUR ANSWER.

Circle only one response for each statement, and respond to all statements. **DO NOT ERASE!** If you need to change an answer, make an "X" through the incorrect answer and circle the correct response. For example:

I enjoy going to the movies.   SA   A   NS   D   SD

Before responding to the statements, write your name, gender, date of birth, ethnic group, marital status. child's name, child's gender, child's date of birth, and today's date in the space at the top of the questionnaire.

SA=Strongly Agree	A=Agree	NS=Not Sure	D=Disagree	SD=Strongly Disagree				

	SA	A	NS	D	SD
1. I often have the feeling that I cannot handle things very well.	SA	A	NS	D	SD
2 I find myself giving up more of my life to meet my children's needs than I ever expected.	SA	A	NS	D	SD
3 I feel trapped by my responsibilities as a parent.	SA	A	NS	D	SD
4 Since having this child I have been unable to do new and different things.	SA	A	NS	D	SD
5 Since having a child, I feel that I am almost never able to do things that I like to do.	SA	A	NS	D	SD
6 I am unhappy with the last purchase of clothing I made for myself.	SA	A	NS	D	SD
7 There are quite a few things that bother me about my life.	SA	A	NS	D	SD
8. Having a child has caused more problems than I expected in my relationship with my spouse (male/female friend).	SA	A	NS	D	SD
9. I feel alone and without friends.	SA	A	NS	D	SD
10. When I go to a party, I usually expect not to enjoy myself.	SA	A	NS	D	SD
11 I am not as interested in people as I used to be.	SA	A	NS	D	SD
12. I don't enjoy things as I used to.	SA	A	NS	D	SD
13. My child rarely does things for me that make me feel good.	SA	A	NS	D	SD
14. Most times I feel that my child does not like me and does not want to be close to me.	SA	A	NS	D	SD
15. My child smiles at me much less that I expected.	SA	A	NS	D	SD
16. When I do things for my child, I get the feeling that my efforts are not appreciated very much.	SA	A	NS	D	SD
17. When playing, my child doesn't often giggle or laugh.	SA	A	NS	D	SD
18. My child doesn't seem to learn as quickly as most children.	SA	A	NS	D	SD
19. My child doesn't seem to smile as much as most children.	SA	A	NS	D	SD
20. My child is not able to do as much as I expected.	SA	A	NS	D	SD
21. It takes a long time & it is very hard for my child to get used to new things.	SA	A	NS	D	SD

For the next statement, choose your response from the choices "1" to "5" below

	1	2	3	4	5
22. I feel that I am: 1. not very good at being a parent	1	2	3	4	5

       2. a person who has some trouble being a parent
       3. an average parent
       4. a better than average parent
       5. a very good parent

	SA	A	NS	D	SD
23. I expected to have closer and warmer feelings for my child than I do and this bothers me.	SA	A	NS	D	SD
24. Sometimes my child does things that bother me just to be mean.	SA	A	NS	D	SD
25. My child seems to cry or fuss more often than most children.	SA	A	NS	D	SD
26. My child generally wakes up in a bad mood.	SA	A	NS	D	SD
27. I feel that my child is very moody and easily upset.	SA	A	NS	D	SD
28. My child does a few things which bother me a great deal.	SA	A	NS	D	SD
29. My child reacts very strongly when something happens that my child doesn't like.	SA	A	NS	D	SD
30. My child gets upset easily over the smallest thing.	SA	A	NS	D	SD
31. My child's sleeping or eating schedule was much harder to establish than I expected.	SA	A	NS	D	SD

For the next statement, choose your response from the choices "1" to "5" below.

	1	2	3	4	5
32. I have found that getting my child to do something or stop doing something is:	1	2	3	4	5

       1. much harder than I expected
       2. somewhat harder than I expected
       3. shout as hard as I expected
       4. somewhat easier than I expected
       5. much easier than 1 expected

For the next statement, choose your response from the choices "10+" to "1-3".

	10+	8-9	6-7	4-5	1-3
33. Think carefully and count the number of things which your child does that bother you. For example: dawdles, refuses to listen, overactive, cries, interrupts, fights, whines, etc.	10+	8-9	6-7	4-5	1-3
34. There are some things my child does that really bother me a lot.	SA	A	NS	D	SD
35. My child turned out to be more of a problem than I had expected.	SA	A	NS	D	SD
36. My child makes more demands on me than most children.	SA	A	NS	D	SD

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

HEALTH SERVICE PROVIDER FORM (Data form 4)

IDENTIFYING DETAILS:

Study Identifier No.: |⎽|⎽|⎽|⎽| - |⎽|⎽|⎽|

Baby surname: _____ Baby first name: _____

Baby medical record number: |⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|⎽|

Baby date of birth: _____/_____/_____
                       day   month   year

DETAILS OF VISIT TO HEALTH SERVICE PROVIDER:

Date(s) of visit: _____/_____/_____
                     day   month   year

Type of provider:

    GP   Nurse home visit

    Routine follow up (at hospital clinic)   Early childhood centre

    Paediatrician (in private rooms)   Other

    Hospital outpatient visit (e.g. emergency department)

Primary reason for visit:

    Routine

    Developmental therapy

    Specific illness

Details of visit: _____

_____

Name of provider: _____

Address of provider: _____

Contact phone of provider: (   )_____

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

RE-HOSPITALISATION FORM (Data form 3)

IDENTIFYING DETAILS:

Study Identifier No.: |__|__|__|__| - |__|__|__|

Baby surname: _____   Baby first name: _____

Baby date of birth: _____/_____/_____
                          day   month   year

DETAILS OF RE-HOSPITALISATION:

Hospital of admission (name): _____

Baby medical record number: |__|__|__|__|__|__|__|__|__|__|__|

Date of admission: _____/_____/_____
                          day   month   year

Date of discharge: _____/_____/_____
                          day   month   year

Principal reason for hospitalisation:

   Surgery   Social problem

    Respiratory illness   Other

    Neurological problem

Details: _____

_____

DRG: |__|__|__| _____

Maximum treatment required: Admitted ICU: yes   no

                                            Mechanical ventilation: yes   no

Other treatment (describe):   _____

BO⊙ST Trial
₂

Benefits Of Oxygen Saturation Targeting Trial

SAMPLE SIZE CALCULATIONS

Using a confidence level of 0.95 and power 0.80, with a 1:1 ratio of treatment to controls, we could detect the following differences with a sample size of approximately 150 subjects in each arm (300 total):

Primary outcomes (growth and development)

1. Mean Griffiths scores:
   Control mean: 101.0
   Treated mean: 105.0
   Standard deviation: 12.0

2. Weight <10th centile at 1 year corrected:
   Percent in Control: 47.0
   Percent in Treated: 30.0   *to reduce from half to less than a third*

3. Mean weight (kg) at 1 year corrected:
   Control mean: 8.8
   Treated mean: 9.3
   Standard deviation: 1.4

4. Mean head circumference (cm) at 1 year corrected:
   Control mean: 46.4
   Treated mean: 47.0
   Standard deviation: 1.8

5. Length <10th centile at 1 year corrected:
   Percent in Control: 40.9
   Percent in Treated: 23.5   *to reduce by half*

6. Mean length (cm) at 1 year corrected:
   Control mean: 72.6
   Treated mean: 73.9
   Standard deviation: 3.8

7. Major developmental abnormality (blindness, deafness, CP, Griffiths score < 2 SD mean) at 1 year corrected:
   Percent in Control: 23.9
   Percent in Treated: 10.0   *to reduce by half*

8. Major developmental abnormality (blindness, deafness, CP, Griffiths score < 2 SD mean) at 1 year corrected (but with normal discharge head ultrasound):
   Percent in Control: 14.0
   Percent in Treated: 4.0   *to reduce by greater than two thirds*

Secondary outcomes

1. Postmenstrual age (weeks) to full sucking feeds:
      Control mean: 35.5
      Treated mean: 35.0   *to reduce time by 0.5 weeks*
      Standard deviation: 1.5   *(significantly reduce costs)*

2. Postmenstrual age (weeks) at end of oxygen therapy:
      Control mean: 35.0
      Treated mean: 35.5   *to increase time by 0.5 weeks*
      Standard deviation: 1.5   *(significantly increase costs)*

3. Lower respiratory illness (rate per year)
      Control mean: 1.6
      Treated mean: 1.0   *to see 33% reduction*
      Standard deviation: 1.7

3. Emergency department visits (rate per year)
      Control mean: 1.9
      Treated mean: 1.0   *to see 50% reduction*
      Standard deviation: 2.7

4. Physicians visits (rate per year)
      Control mean: 10.3
      Treated mean: 7.3   *to see 33% reduction*
      Standard deviation: 8.7

5. Hospitalisations due to lower respiratory illness (rate per year)
      Control mean: 1.0
      Treated mean: 0.7   *to see 33% reduction*
      Standard deviation: 1.0

6. Postnatal depression: proportion with high postnatal depression scores
      Percent in Control: 15.0   *may see increase in*
      Percent in Treated: 30.0   *postnatal depression*

7. Parent stress: proportion with high parenting stress scores
      Percent in Control: 10.0   *may see increase in*
      Percent in Treated: 23.0   *parental stress*

8. Family impact: proportion with high family impact scores
      Percent in Control: 12.0   *may see increase in*
      Percent in Treated: 25.0   *impact on families*

9. Infant temperament: proportion of "easy" babies
      Percent in Control: 10.0   *may see improvement in*
      Percent in Treated: 23.0   *infant temperament*

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

DATA REPORT TO SAFETY MONITORING COMMITTEE

Cut off date for data for this report: _____ / _____ / _____

This report relates to data analysed after approximately:

☑ **5 months from commencement**

☐ **75 subjects enrolled**

☐ **150 subjects enrolled**

☐ **225 subjects enrolled**

☐ **300 subjects enrolled**

N. B. Data pertains to the first 75 subjects who *were enrolled and have reached 38 weeks pma.* **This covers the time period 16/9/96 to 4/9/97.**

Table 1

Total No. subjects	Number enrolled	Percent (%) of total
Group A		%
Group B		%
Total		100 %

Retinopathy of prematurity (ROP) Grades 3 or 4 to 38 weeks postmenstrual age (pma)

Table 2

No. of subjects with **Grade 3/4 ROP at 38 weeks pma** by gestational age (GA) strata				
	24-27 weeks GA	28-29 weeks GA	Total No.	Cumulative Incidence %
Group A				
Group B				
Total No.				

Statistical analyses performed :

Proportion of Grade 3/4 ROP to 38 weeks pma in Group A   compared with   proportion of Grade 3/4 ROP to 38 weeks pma in Group B:

p value (2 sided): _____ Test statistic used: _____

Mortality to 38 weeks postmenstrual age (pma)

Table 3

No. of deaths to 38 weeks pma by gestational age (GA) strata				
	24-27 weeks GA	28-29 weeks GA	Total No.	Cumulative Incidence %
Group A				
Group B				
Total No.				

Statistical analyses performed :

Proportion of deaths to 38 weeks pma in Group A   compared with   proportion of deaths to 38 weeks pma in Group B:

p value (2 sided): _____ Test statistic used: _____

Analysis and report provided by: _____
<div align="center">Print name</div>

<div align="center">_____</div>
<div align="center">Signature</div>

<div align="center">_____ / _____ / _____</div>
<div align="center">Date</div>

Please forward a copy of this analysis to:

      * Prof Craig Mellis
        Dept. of Respiratory Medicine
        New Childrens Hospital, Westmead. NSW. 2145.

      * Dr Andrew Berry
        State Medical Director NETS
        POB 563, Wentworthville. NSW. 2145.

      * Dr Frank Martin
        Dept. of Ophthalmology
        New Childrens Hospital, Westmead. NSW. 2145.

BO₂ST Trial

Benefits Of Oxygen Saturation Targeting Trial

REPORT BY THE SAFETY MONITORING COMMITTEE

Meeting held: _____ / _____ / _____
<div align="center">Date</div>

Venue: _____

Present: _____

_____

_____

Cut off date for data for this report: _____ / _____ / _____
<div align="center">Date</div>

This relates to data analysed after approximately:

- ☑ **5 months from commencement**
- ☐ **75 subjects enrolled**
- ☐ **150 subjects enrolled**
- ☐ **225 subjects enrolled**
- ☐ **300 subjects enrolled**

Comments by Safety Monitoring Committee Chairperson:

Recommendations by Safety Monitoring Committee:

Name: _____

Signature: _____

Date: _____ / _____ / _____

Please forward this report to: Lisa Askie, BOOST Trial Coordinator
                             NSW Centre for Perinatal Health Service Research,
                 Building D02, University of Sydney. NSW. 2006.

Table 20:   Selected outcomes for all infants, by treatment group, adjusted for known prognostic factors

Variable	SpO$_2$ 91-94% Control group N=178	SpO$_2$ 95-98% Treatment group N=180	Median (MedD) or Mean Difference (MD) [95% CI]
Length of stay, after randomisation (days)	50.0 (IQR 39-60)	50.0 (IQR 42-61.5)	MedD 2 [-1, 5] P=0.2 *(adjusted P=0.07)* ±
pma at discharge (weeks)	39.1 (IQR 37-40)	39.1 (IQR 38-41)	MedD 0.3 [-0.1, 0.9] P=0.2 *(adjusted P=0.08)* ±
pma at full sucking feeds (weeks)	37.7 (IQR 37-39)	37.7 (IQR 36-39)	MedD -0.4 [-0.9, 0] P=0.9 *(adjusted P=0.6)* ±
Days assisted ventilation (all types), after randomisation - only if ventilation ended after randomisation	14.0 (IQR 7-28)	14.0 (IQR 6-35)	MedD 0 [-4, 4] P=0.9 *(adjusted P=0.9)* ±
Mean weight at 12 months corrected age	9.10kg (SD 1.5)	9.25kg (SD 1.6)	MD 0.15kg [-0.18, 0.49] P=0.4 *(adjusted P=0.3)* ⊕
Mean Revised Griffiths score at 12 months corrected age	88.3 (SD 18.3)	86.8 (SD 21.8)	MD -1.5 [-5.9, 2.9] P=0.5 *(adjusted P=0.3)* ⊕

± *adjusted for gestational age, sex, maternal ethnicity, plurality (singleton vs multiple) using multiple regression*
⊕ *adjusted for baseline Edinburgh Postnatal Depression Scale score in addition to ± variables*

Table 21:   Selected outcomes for <28 week gestation infants only, by treatment group, adjusted for known prognostic factors

Variable	SpO$_2$ 91-94% Control group N=124	SpO$_2$ 95-98% Treatment group N=132	Relative Risk or Median Difference [95% CI]
ROP treatment	20 (16.1%)	11 (8.3%)	RR 0.52 [0.26, 1.03] P=0.06+
Length of stay, after randomisation (days)	51.0 (IQR 41-62)	51.0 (IQR 42-62)	MedD 1 [-3, 5] P=0.5 *(adjusted P=0.2)* ±
pma at discharge (weeks)	39.5 (IQR 38-41)	39.1 (IQR 38-41)	MedD 0.3 [-0.3, 0.9] P=0.4 *(adjusted P=0.2)* ±
pma at full sucking feeds (weeks)	38.1 (IQR 37-39)	37.9 (IQR 36-39)	MedD -0.7 [-1.3, -0.1] P=0.6 *(adjusted P=0.6)* ±
Days assisted ventilation (all types), after randomisation - only if end ventilation after randomisation	14.5 (IQR 8-28) N=62	14.0 (IQR 6-29), N=64	MedD -1 [-6, 4] P=0.7 *(adjusted P=0.4)* ±

+ *when adjusted for gestational age, sex, maternal ethnicity, and plurality (singleton vs multiple) using logistic regression RR 0.42 [95% CI 0.17, 1.05] P=0.06*

± *adjusted for gestational age, sex, maternal ethnicity, and plurality (singleton vs multiple) using multiple regression*

BO**2**ST Trial

Benefits Of Oxygen Saturation Targeting Trial

MAJOR OUTCOMES, STRATIFIED BY CENTRE

Experimental group = SpO_2 **95-98%**
Control group = SpO_2 **91-94%**

Analyses: experimental/control (RR, 95% CI)

1. Canberra Hospital

Variable	SpO_2 91-94% Control gp N=15	SpO_2 95-98% Treatment gp N=15	RR [95% CI]
Wt <10th centile at 12 mth corr	6 (40.0%, N=15)	4 (26.7%, N=15)	0.67 [0.23, 1.89]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	2 (13.3%, N=15)	3 (20.0%, N=15)	1.5 [0.296, 7.73]
Supplemental O_2 at 36 wks pma	6 (40.0%)	11 (73.3%)	1.83 [0.92, 3.66]
Home oxygen	2 (13.3%)	8 (53.3%)	4.00 [1.01, 15.81]

2. John Hunter Hospital

Variable	SpO_2 91-94% Control gp N=37	SpO_2 95-98% Treatment gp N=35	RR [95% CI]
Wt <10th centile at 12 mth corr	10 (32.3%, N=31)	11 (35.5%, N=31)	1.10 [0.55, 2.21]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	13 (41.9%, N=31)	8 (25.8%, N=31)	0.62 [0.30, 1.27]
Supplemental O_2 at 36 wks pma	17 (45.9%)	26 (74.3%)	1.62 [1.08, 2.41]
Home oxygen	5 (13.5%)	10 (28.6%)	2.11 [0.80, 5.57]

3. King George V Hospital

Variable	SpO_2 91-94% Control gp N=38	SpO_2 95-98% Treatment gp N=43	RR [95% CI]
Wt <10th centile at 12 mth corr	11 (29.7%, N=37)	14 (34.1%, N=41)	1.15 [0.60, 2.21]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	5 (13.5%, N=37)	5 (12.2%, N=41)	0.90 [0.28, 2.87]
Supplemental O_2 at 36 wks pma	19 (50%)	26 (60.5%)	1.21 [0.81, 1.80]
Home oxygen	5 (13.2%)	7 (16.3%)	1.24 [0.43, 3.58]

4. Liverpool Hospital

Variable	SpO$_2$ 91-94% Control gp N=16	SpO$_2$ 95-98% Treatment gp N=13	RR [95% CI]
Wt <10th centile at 12 mth corr	7 (53.8%, N=13)	4 (30.8%, N=10)	0.74 [0.30, 1.85]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	1 (7.1%, N=14)	2 (20%, N=10)	2.80 [0.29, 26.81]
Supplemental O$_2$ at 36 wks pma	9 (56.3%)	9 (69.2%)	1.23 [0.70, 2.16]
Home oxygen	1 (6.3%)	1 (7.7%)	1.23 [0.08, 17.83]

5. Mater Mothers' Hospital

Variable	SpO$_2$ 91-94% Control gp N=23	SpO$_2$ 95-98% Treatment gp N=20	RR [95% CI]
Wt <10th centile at 12 mth corr	9 (40.9%, N=22)	5 (25.0%, N=20)	0.61 [0.25, 1.52]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	4 (18.2%, N=22)	2 (10.0%, N=20)	0.55 [0.11, 2.69]
Supplemental O$_2$ at 36 wks pma	8 (34.8%)	12 (60.0%)	1.72 [0.89, 3.35]
Home oxygen	7 (30.4%)	9 (45.0%)	1.48 [0.67, 3.24]

6. Nepean Hospital

Variable	SpO$_2$ 91-94% Control gp N=25	SpO$_2$ 95-98% Treatment gp N=24	RR [95% CI]
Wt <10th centile at 12 mth corr	5 (21.7%, N=23)	10 (43.5%, N=23)	2.00 [0.81, 4.94]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	8 (34.8%, N=23)	8 (34.8%, N=23)	1.00 [0.45, 2.21]
Supplemental O$_2$ at 36 wks pma	11 (44.0%)	10 (41.7%)	0.95 [0.50, 1.81]
Home oxygen	4 (16.0%)	4 (16.7%)	1.04 [0.29, 3.70]

7. Royal Hospital for Women

Variable	SpO$_2$ 91-94% Control gp N=3	SpO$_2$ 95-98% Treatment gp N=6	RR [95% CI]
Wt <10th centile at 12 mth corr	2 (66.7%, N=3)	3 (50.0%, N=6)	0.75 [0.24, 2.33]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	1 (33.3%, N=3)	0 (0%, N=6)	0.19 [0.01, 3.66]
Supplemental O$_2$ at 36 wks pma	2 (66.7%)	5 (83.3%)	1.25 [0.52, 3.00]
Home oxygen	0 (0%)	0 (0%)	not estimable

8. Royal North Shore Hospital

Variable	SpO$_2$ 91-94% Control gp N=21	SpO$_2$ 95-98% Treatment gp N=24	RR [95% CI]
Wt <10th centile at 12 mth corr	11 (52.4%, N=21)	4 (18.2%, N=22)	0.35 [0.13, 0.92]
Major developmental abn at 12 mth corr (CP or blind or DQ <2SD below mean)	6 (28.6%, N=21)	11 (50.0%, N=22)	1.75 [0.79, 3.88]
Supplemental O$_2$ at 36 wks pma	10 (47.6%)	17 (70.8%)	1.49 [0.89, 2.49]
Home oxygen	6 (28.6%)	15 (62.5%)	2.19 [1.04, 4.60]

SUMMARY GRAPHS: major outcomes, stratified by centre

Weight <10th centile at 12 months corrected age, by centre

Study	higher O2 n/N	standard O2 n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Canberra	4 / 15	6 / 15		9.8	0.67[0.23,1.89]
JHH	11 / 31	10 / 31		16.4	1.10[0.55,2.21]
KGV	14 / 41	11 / 37		18.9	1.15[0.60,2.21]
Liverpool	4 / 10	7 / 13		10.0	0.74[0.30,1.85]
MMH	5 / 20	9 / 22		14.0	0.61[0.25,1.52]
Nepean	10 / 23	5 / 23		8.2	2.00[0.81,4.94]
RHW	3 / 6	2 / 3		4.4	0.75[0.24,2.33]
RNSH	4 / 22	11 / 21		18.4	0.35[0.13,0.92]
Total(95%CI)	55 / 168	61 / 165		100.0	0.88[0.65,1.19]

Test for heterogeneity chi-square=8.79 df=7 p=0.27
Test for overall effect z=-0.82 p=0.4

```
        .1    .2           1        5   10
        Favours higher O2     Favours standard O2
```

Major developmental abnormality at 12 months corrected age, by centre

Study	higher O2 n/N	standard O2 n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Canberra	3 / 15	2 / 15		4.9	1.50[0.29,7.73]
JHH	8 / 31	13 / 31		31.7	0.62[0.30,1.27]
KGV	5 / 41	5 / 37		12.8	0.90[0.28,2.87]
Liverpool	2 / 10	1 / 14		2.0	2.80[0.29,26.81]
MMH	2 / 20	4 / 22		9.3	0.55[0.11,2.69]
Nepean	8 / 23	8 / 23		19.5	1.00[0.45,2.21]
RHW	0 / 6	1 / 3		4.7	0.19[0.01,3.66]
RNSH	11 / 22	6 / 21		15.0	1.75[0.79,3.88]
Total(95%CI)	39 / 168	40 / 166		100.0	0.96[0.66,1.39]

Test for heterogeneity chi-square=6.42 df=7 p=0.49
Test for overall effect z=-0.22 p=0.8

```
        .1    .2           1        5   10
        Favours higher O2     Favours standard O2
```

3

Oxygen dependent at 36 weeks pma, by centre

Study	higher O2 n/N	standard O2 n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Canberra	11 / 15	6 / 15		7.3	1.83[0.92,3.66]
JHH	26 / 35	17 / 37		20.1	1.62[1.08,2.41]
KGV	26 / 43	19 / 38		24.5	1.21[0.81,1.80]
Liverpool	9 / 13	9 / 16		9.8	1.23[0.70,2.16]
MMH	12 / 20	8 / 23		9.0	1.72[0.89,3.35]
Nepean	10 / 24	11 / 25		13.1	0.95[0.50,1.81]
RHW	5 / 6	2 / 3		3.2	1.25[0.52,3.00]
RNSH	17 / 24	10 / 21		13.0	1.49[0.89,2.49]
Total(95%CI)	116 / 180	82 / 178		100.0	1.39[1.15,1.68]

Test for heterogeneity chi-square=3.69 df=7 p=0.82
Test for overall effect z=3.35 p=0.0008

.1   .2   1   5   10
Favours higher O2   Favours standard O2

Home oxygen, by centre

Study	higher O2 n/N	standard O2 n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
Canberra	8 / 15	2 / 15		6.7	4.00[1.01,15.81]
JHH	10 / 35	5 / 37		16.3	2.11[0.80,5.57]
KGV	7 / 43	5 / 38		17.8	1.24[0.43,3.58]
Liverpool	1 / 13	1 / 16		3.0	1.23[0.08,17.83]
MMH	9 / 20	7 / 23		21.8	1.48[0.67,3.24]
Nepean	4 / 24	4 / 25		13.1	1.04[0.29,3.70]
x RHW	0 / 6	0 / 3		0.0	Not Estimable
RNSH	15 / 24	6 / 21		21.4	2.19[1.04,4.60]
Total(95%CI)	54 / 180	30 / 178		100.0	1.79[1.22,2.64]

Test for heterogeneity chi-square=3.18 df=6 p=0.79
Test for overall effect z=2.98 p=0.003

.1   .2   1   5   10
Favours higher O2   Favours standard O2

4

BOO_2ST Trial

Benefits Of Oxygen Saturation Targeting Trial

SENSITIVITY ANALYSIS WITH RANDOM REMOVAL OF 50% OF RELATED MULTIPLES

Experimental group = **SpO$_2$ 95-98%**
Control group = **SpO$_2$ 91-94%**

Analyses: experimental/control (RR, 95% CI)

Sensitivity analysis with random 50% of related multiples[+] removed

Variable	SpO$_2$ 91-94% Control gp N=167	SpO$_2$ 95-98% Treatment gp N=166	RR [95% CI] P value
Wt <10th centile @ 12 mth	57 (40.1%, N=142)	52 (35.9%, N=145)	0.89 [0.66, 1.20] p=0.46
Major dev abn @ 12 mth corr (CP or blind or DQ <2SD below mean)	43 (27.7%, N=155)	39 (25.3%, N=154)	0.91 [0.63, 1.32] p=0.63
Supplemental O$_2$ at 36 wks pma	79 (47.3%)	109 (65.7%)	1.39 [1.14, 1.69] p=0.0007
Home oxygen	30 (18.0%)	52 (31.3%)	1.74 [1.18, 2.59] p=0.005

+ **Related multiple** = pair of infants from the same birth: one infant of the pair was randomised, the second infant was allocated to the same treatment group as their sibling. There were 25 pairs of related multiples (total n=50) enrolled (see Table 4).

List of published papers and abstracts arising from this thesis

1. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM, on behalf of the BOOST Trial collaborators group. The effect of differing oxygen saturation targeting ranges on long term growth and development of extremely preterm, oxygen dependent infants: the BOOST Trial. *Proceedings of the 6th Annual Congress of Perinatal Society of Australia & New Zealand and the Federation of the Asia and Oceania Perinatal Societies 12th Congress*, 2002, Christchurch, New Zealand, oral presentation A133/134.

2. Jones RA, Askie LM. Variation in support and services for infants receiving home oxygen therapy. *Proceedings of the 6th Annual Congress of Perinatal Society of Australia & New Zealand and the Federation of the Asia and Oceania Perinatal Societies 12th Congress*, 2002, Christchurch, New Zealand, poster presentation P144.

3. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. The effect of differing oxygen saturation targeting ranges on long term growth and development of extremely preterm, oxygen dependent infants: the BOOST Trial [abstract]. Pediatric Research 2002; 51 (4): 378A.

4. Askie LM, Henderson-Smart DJ, Irwig, L, Simpson JM. Growth and development of extremely preterm infants randomized to standard or higher oxygen saturation targeting: the BOOST trial. Submitted manuscript November 2002 to The New England Journal of Medicine; status: manuscript under review.

5.   Askie LM, Jones RA, Henderson-Smart DJ. Health service utilisation and rehospitalisation outcomes for home oxygen infants in the first year of life. Submitted to *7th Annual Congress of Perinatal Society of Australia & New Zealand and the Federation of the Asia and Oceania Perinatal Societies 12ᵗʰ Congress*, 2003, Hobart, Australia; poster presentation P11.

6.   Lloyd B, Jones R, Askie LM. The impact and support needs of families with an infant on home oxygen therapy: a qualitative study. Submitted to *7th Annual Congress of Perinatal Society of Australia & New Zealand and the Federation of the Asia and Oceania Perinatal Societies 12ᵗʰ Congress,* 2003, Hobart, Australia; oral presentation A69.

7.   Foster J, Todd D, Askie L, Wade K, Bidewell J. Pulse oximetry: a comparison of two different brands in relation to oxygen saturation and arterial partial pressure of oxygen. *Proceedings of the 4th Annual Congress of Perinatal Society of Australia & New Zealand and the 7th Annual Australian Neonatal Nurses Association Conference*, 2000, Brisbane, oral presentation A59.

8.   Askie L, Henderson-Smart DJ. Early versus late discontinuation of oxygen in preterm or low birth weight infants. In: *The Cochrane Library*, Issue 4, 2002. Oxford: Update Software.

9.   Askie L, Henderson-Smart DJ. Gradual versus abrupt discontinuation of oxygen in preterm or low birth weight infants. In: *The Cochrane Library*, Issue 4, 2002. Oxford: Update Software.

10. Askie L, Henderson-Smart DJ. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. In: *The Cochrane Library*, Issue 1, 2003. Oxford: Update Software.

11. Lloyd J, Askie L, Smith J, Tarnow-Mordi W. Supplemental oxygen in the treatment of retinopathy of prematurity [protocol]. In: *The Cochrane Library*, Issue 4, 2002. Oxford: Update Software.