Outcome after Selective Early Treatment for Closure of Patent Ductus ARteriosus in Preterm Babies

PROTOCOL

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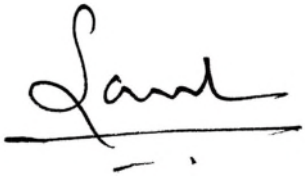

26/01/15

Chief Investigator | Chief Investigator's Signature | Date

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1. Protocol Synopsis

Trial Title:	Outcome after Selective Early Treatment for Closure of Patent Ductus ARteriosus in Preterm Babies [Baby-OSCAR Trial]
Internal Reference:	Baby-OSCAR
Clinical Phase:	Phase III
Trial Design:	Multi-centre, masked, randomised placebo-controlled parallel group trial to determine short and long term health and economic outcomes of the treatment of a large Patent Ductus Arteriosus (PDA) in extremely preterm babies with ibuprofen within 72 hours of birth. The main trial will be conducted after an internal pilot phase, which will be run to assess the suitability of trial procedures and likelihood of recruitment targets being achieved.
Trial Participants:	Extreme preterm babies with a large PDA confirmed using echocardiography.
Inclusion Criteria:	Babies will be considered eligible for inclusion in the trial if they are: • Born at 23^{+0} to 28^{+6} weeks of gestation • Less than 72 hours old • Confirmed by echocardiography to have a large PDA which - is at least 1.5 mm in diameter (determined by gain optimised colour Doppler), *and* - has unrestrictive pulsatile left to right flow (ratio of flow velocity in PDA Maximum (V_{max}) to Minimum (V_{min}) > 2:1)) In addition: • The responsible clinician is uncertain about whether the baby might benefit from treatment to close the PDA • Written informed consent has been obtained from the parent(s).
Exclusion Criteria:	Babies will be excluded from participation in the trial if they have: • No realistic prospect of survival • Severe congenital anomaly • Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen • Other conditions that would contraindicate the use of ibuprofen (Clinically significant intracranial or gastrointestinal haemorrhage,

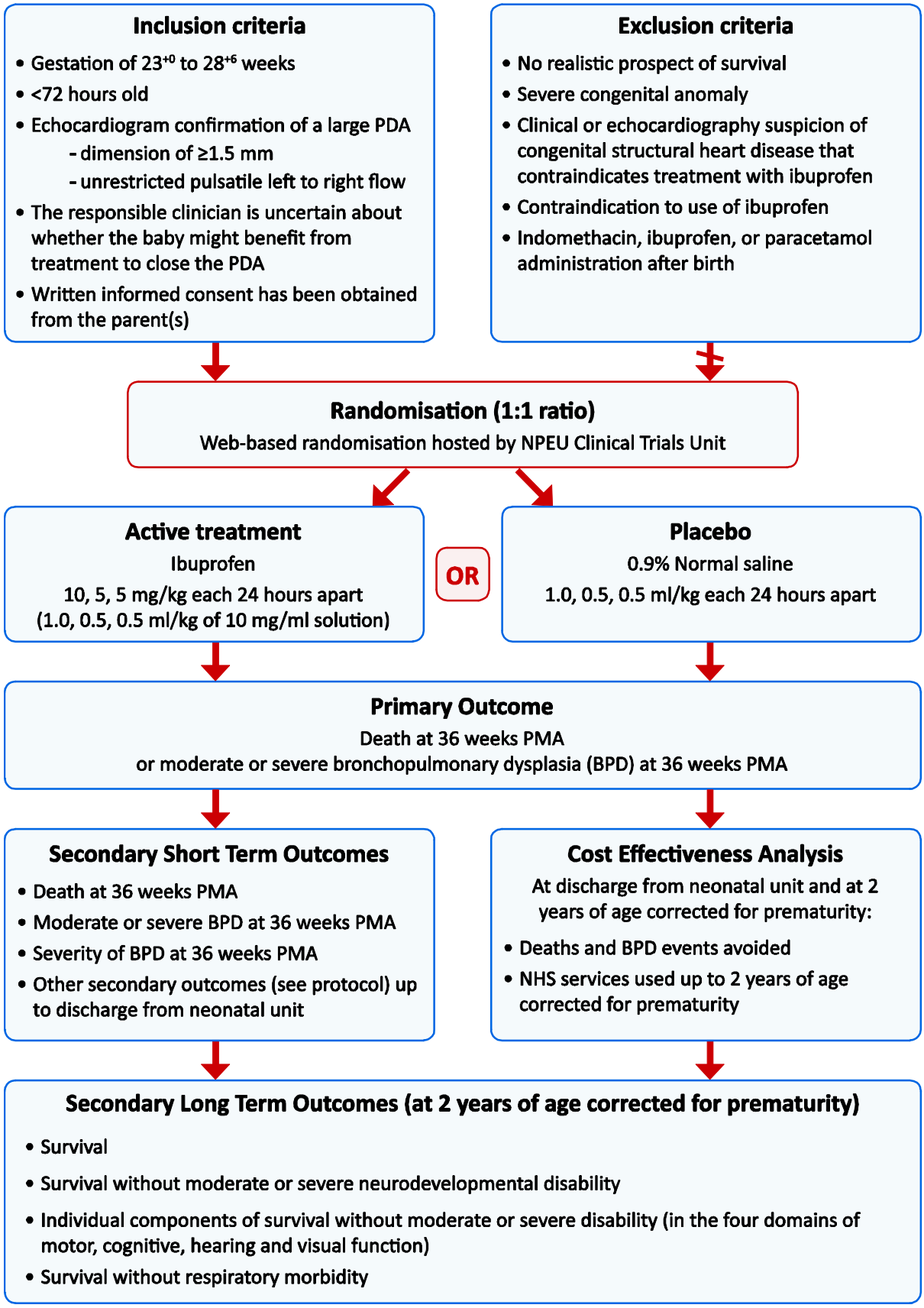
	coagulopathy, thrombocytopenia (platelet count <50,000), renal failure, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC)) • Indomethacin, ibuprofen, or paracetamol administration after birth
Sample Size:	Approximately 730 preterm babies in total (including those recruited during the internal pilot phase). 365 babies per treatment arm.
Trial Sites:	25 UK tertiary (level 3) neonatal units. 4 sites for the internal pilot phase.
Trial Period:	Trial period for an individual baby is defined as randomisation to 2 years of age corrected for prematurity. For the purposes of regulatory notification, end of trial is defined as the last follow-up assessment at 2 years of age corrected for prematurity. The entire trial is anticipated to take 82 months to complete (including set-up, internal pilot phase and reporting). Adverse Events which are serious will be recorded from first dose until 7 days after trial medication. Only Unforeseeable SAEs will be reported.
Primary Objective:	To determine if the selective treatment of echocardiographically confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth reduces the incidence of death at 36 weeks postmenstrual age, or moderate or severe bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age.
Primary Endpoints:	Composite outcome of incidence of death at 36 weeks postmenstrual age, or moderate or severe BPD at 36 weeks postmenstrual age.
Secondary Objectives:	To determine if the selective treatment of confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth results in: • A reduction in the components of the primary outcome, the duration of ventilation, acute morbidities including necrotising enterocolitis (Bell stage 2 or 3), severe intraventricular haemorrhage (grade 3 or 4), cystic periventricular leukomalacia, retinopathy of prematurity (requiring treatment), failure of PDA closure requiring rescue treatment, side effects of drug treatment, gastrointestinal bleeding and the duration of intensive care (short-term secondary objectives). • Improved health outcomes at 2 years corrected age including survival without moderate or severe neurodevelopmental disability (long-term primary objective) and survival without respiratory morbidity (long-

	term secondary objective). An economic evaluation will be carried out from the perspective of the health service. It will take the form of a cost-effectiveness analysis presented in terms of cost per major outcome averted (MOA). The major outcomes are those of the primary outcome, namely death and any moderate or severe BPD at 36 weeks postmenstrual age. Additional analyses will take place on a range of secondary outcomes and on neurodevelopmental outcomes at 2 years. The incremental cost estimate for statistically significant differences in the pre-specified outcomes in primary and subgroup analyses would be computed.
Secondary Endpoints:	**Short Term Outcomes** • Death at 36 weeks postmenstrual age • Moderate or severe BPD at 36 weeks postmenstrual age • Severity of BPD at 36 weeks postmenstrual age (see table in Section 6.5) Incidence or duration of the following up to discharge: • Severe intraventricular haemorrhage (IVH) (grade 3/4 with ventricular dilation or intraparenchymal bleeding) • Cystic periventricular leukomalacia (PVL) • Retinopathy of prematurity (ROP) requiring treatment • Significant pulmonary haemorrhage (fresh blood in ET tube with increase in respiratory support) • Pulmonary hypertension requiring treatment with pulmonary vasodilator • NEC definitive and/or complicated (Bell stage II and above) confirmed by radiography and / or histopathology • NEC requiring surgery • Gastrointestinal bleeding within 7 days of the first dose of trial drug administration • Spontaneous intestinal perforation • Closed or non-significant PDA (<1.5 mm) at 3 weeks of age, confirmed by ECHO (or hospital discharge from recruiting centre, if discharged sooner) • PDA $\geq$ 1.5 mm at 3 weeks, not treated medically or by surgical closure • Medical rescue treatment of a symptomatic PDA with a COX

	inhibitor • Rescue treatment of a symptomatic PDA by surgical treatment • Administration and duration of inotropic support • Total duration of respiratory support a) Invasive Ventilation through an endotracheal tube b) Non-invasive support through nasal CPAP, nasal ventilation, or high flow oxygen therapy • Discharge home on oxygen • Duration of initial hospitalisation (birth to discharge home) • Postnatal steroid use for chronic lung disease • Tolerance of ibuprofen treatment within the safety reporting range described in the protocol (Section 9) **Long Term Outcomes** Secondary long term clinical outcomes assessed at 2 years of age corrected for prematurity: • Survival • Survival without moderate or severe neurodevelopmental disability • Individual components of survival without moderate or severe neurodevelopmental disability (in the four domains of motor, cognitive, hearing and visual function). Cognitive disability will be assessed by determining the Parent Report Composite score obtained through the Parent Report of Cognitive Abilities-Revised (PARCA-R) assessment. The PARCA-R assessment will be adapted to include questions to assess hearing and visual function. Motor function will be assessed using the Gross Motor Function Classification System. • Respiratory morbidity. Respiratory morbidity will be assessed by the need for oxygen or respiratory support; presence of persistent cough and/or wheeze; need for regular treatment for respiratory illness; unscheduled attendances at hospital/GP; number of re-hospitalisation episodes and duration. A cost-effectiveness analysis will be conducted of deaths and BPD events avoided and national health services used up to 2 years of age corrected for prematurity.
Process Outcomes	Process outcomes will be the following; • Number of doses of trial medication received

	• Adherence to protocol (e.g. protocol violations, incidence of non-symptomatic rescue treatment etc.) • Study withdrawals
Investigational Medicinal Product:	Ibuprofen will be provided as a clear sterile preservative-free solution for intravenous injection. An initial dose of 10 mg/kg will be followed by two doses of 5 mg/kg at 24 and 48 hours after the initial dose. The solution of ibuprofen is provided at a concentration of 10 mg/ml in a single-use vial, thus 1 ml/kg, followed by two administrations of 0.5 ml/kg will be required. Placebo will be provided as a clear sterile solution of 0.9% normal saline. The solution will be indistinguishable from that of ibuprofen. It will be given as a 1 ml/kg infusion followed by two infusions of 0.5 ml/kg at 24 and 48 hours. Doses to be calculated on birth weight and administered as a short infusion over 15 minutes, diluted to appropriate volume with dextrose or saline and first dose administered soon after randomisation and within 72 hours of birth. Rescue treatment will be permitted if defined clinical and echocardiography criteria are met.

2. Trial Flow Diagram



3. Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ARR	Absolute Risk Reduction
BPD	Bronchopulmonary Dysplasia
CI	Chief Investigator
CIG	Co-Investigator Group
COX	Cyclo-oxygenase
CPAP	Continuous Positive Airway Pressure
DA	Ductus Arteriosus
DCF	Data Collection Form
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GMFCS	Gross Motor Function Classification System
GP	General Practitioner
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ITT	Intention to Treat
IVH	Intraventricular Haemorrhage
LCRN	Local Clinical Research Network
LRN	Local Research Nurse
MCRN	Medicines for Children Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
nCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotising Enterocolitis
NHS	National Health Service
NIHR	National Institute for Health Research
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit

NSAID	Non-Steroidal Anti-inflammatory Drug
OR	Odds ratio
PARCA-R	Parent Report of Cognitive Abilities-Revised
PDA	Patent Ductus Arteriosus
PI	Principal Investigator
PIL	Parent Information Leaflet
PMA	Postmenstrual Age
PMG	Project Management Group
PVL	Cystic Periventricular leukomalacia
R&D	NHS Trust Research and Development Department
REC	Research Ethics Committee
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee

4. Introduction

4.1. Background and Rationale

The Ductus Arteriosus (DA) is a vessel that allows blood from the right ventricle to bypass the fetal lungs to the placenta. In term babies it closes spontaneously after birth when breathing is established and is structurally closed after a few days. However, in a large number of preterm babies, the vessel does not close spontaneously resulting in a condition known as Patent Ductus Arteriosus (PDA). Around 7,000 extremely preterm babies (<29 weeks of gestation) are born in the UK every year. In 40% the PDA will fail to close spontaneously even by 4 months of age. [Nemerofsky et al, 2008].

PDA is associated with a number of serious and life-threatening short and long term complications including low blood pressure (hypotension), bleeding in the lungs (pulmonary haemorrhage) and brain (intraventricular haemorrhage (IVH)), systemic complications such as necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and long term health problems such as neurodevelopmental disability and chronic respiratory problems. The persistence of PDA is associated with an 8-fold rise in neonatal mortality [Noori S et al, 2009]. In addition, as PDA is very common in extreme preterm babies and is associated with a prolonged need for respiratory support and hospitalisation, it places a significant financial burden on the National Health Service (NHS).

Historically, clinicians who have been concerned about the complications associated with a PDA have attempted to close PDAs utilising medical (pharmacological) or surgical treatment. Traditionally, medical treatment is instituted as prophylactic treatment (within 24 hours of birth) or symptomatic treatment (usually 5−7 days after birth). Prophylactic pharmacological treatment of all preterm babies unnecessarily exposes a large proportion of babies to the potentially serious side effects of drug treatment, when their PDA would have closed spontaneously. Symptomatic treatment on the contrary delays treatment while waiting for symptoms to appear and could result in a loss of treatment benefit as irreversible damage may have already been done.

Moreover, the practice of a conservative approach of not treating, seems to originate from uncertainty regarding the management of PDA rather than evidence favouring no intervention. This is due to the fact that most studies conducted to date have involved more mature preterm babies (over 1,000 g or 28 weeks of gestation) whose PDA is more likely to close spontaneously. The studies were also largely designed to assess PDA closure rates rather than clinically important outcomes.

It is now suggested that large PDAs (those with a diameter of ≥1.5 mm) through which blood flow is pulsatile and unrestricted are less likely to close spontaneously. Targeted early

treatment of large PDAs whilst asymptomatic has the potential to overcome the disadvantages of both the prophylactic and symptomatic approaches. Although clinical detection of PDA whilst asymptomatic is challenging, it can be assessed using bedside echocardiography.

Non-steroidal anti-inflammatory drugs, especially indomethacin and ibuprofen have been widely used for the treatment of PDA. Short term efficacy of indomethacin and ibuprofen are equivalent in the treatment of PDA [Su BH et al, 2008]. Ibuprofen however appears to reduce the risk of NEC and is associated with fewer clinical gastrointestinal and renal side effects compared to indomethacin, hence it is the drug of choice for this trial. Paracetamol, has also been recently reported in case studies for closure of symptomatic PDA but further research needs to be done to establish its effectiveness [Oncel MY et al, 2013].

The aim of this trial is to examine whether the pharmacological closure of a large PDA (identified by echocardiography) in extremely preterm babies whilst asymptomatic has a clinically important impact on both short and long term health and economic outcomes.

4.2. Current Evidence Supporting Trial Rationale

Although the number of extremely preterm babies that survive has increased due to improvements in neonatal care, the proportion of babies with moderate or severe disability has remained largely unchanged. Concern regarding this is reflected in the results of a survey conducted by the Medicines for Children Research Network (MCRN) which identified PDA and BPD as key areas in which clinicians believed further evidence and research is most needed.

To date, the majority of studies of prophylactic or symptomatic treatment of PDA have included babies up to 34 weeks of gestation, have been small in size, were designed to assess PDA closure rates rather than short or long term clinical outcomes and are now relatively old, all of which limit the ability to draw meaningful conclusions from the results. Furthermore, there are no recent trials reporting outcomes after selective early treatment of PDA based both on duct size and haemodynamic assessment. Thus the current literature falls short of providing substantive evidence on the management of PDA among extreme preterm babies leading to uncertainty and heterogeneity in clinical practices.

A recent cohort trial identified presence of a large PDA (defined as a PDA dimension of ≥1.5 mm) on day 3 in babies born before 28 weeks of gestation with threefold increase in odds of death or severe morbidity compared with neonates without PDA (Odds Ratio (OR) 3.4; 95% Confidence Interval (CI) 1.1 to 11.0). Neonates with a large PDA were also reported to have increased odds of IVH (OR 4.2; 95% CI 1.3 to 14.0) and BPD (OR 3.7; 95% CI 1.0 to 14.0) compared with neonates with no PDA [Sellmer A et al, 2013]. In preclinical trials,

pharmacologic PDA closure is reported to improve alveolarisation and minimise the impaired postnatal alveolar development that is the pathologic hallmark of ‘‘new bronchopulmonary dysplasia (BPD)” [Clyman RI, 2013]. An early selective treatment approach for closure of a PDA is suggested to trial its effect on BPD, which is the hypothesis of this trial.

Both indomethacin and ibuprofen have been shown to have comparable efficacy in closing PDA. The relative risks of treatment strategies adapted from the Cochrane Collaboration reviews are outlined in this table [Fowlie PW, 2010; Ohlsson A, 2011; Ohlsson A, 2010; Cooke I, 2009].

		Relative risk (95% Confidence interval)						^^
Author	Intervention	Symptomatic PDA	Death before 36 Weeks	BPD at 36 weeks	NEC	Severe IVH	Death / Severe Disability 18–24 Months	Duration of Ventilation (days)
Fowlie PW, *Cochrane Review* 2010, comparison 1	Prophylactic indomethacin	0.44 (0.38, 0.50)*	0.82 (0.65, 1.03)	1.06 (0.92, 1.22)	1.09 (0.82, 1.46)	0.66 (0.53, 0.82)*	1.02 (0.90, 1.15)	-1.83 (-5.53, 1.87)
Ohlsson A, *Cochrane Review* 2011, comparison 1	Prophylactic ibuprofen	0.17 (0.11, 0.26)*	0.90 (0.62, 1.30)	1.04 (0.87, 1.25)	1.04 (0.63, 1.70)	0.82 (0.54, 1.26)	-	1.02 (-1.99, 4.03)
Ohlsson A, *Cochrane Review* 2010, comparison 2	Symptomatic PDA (indomethacin vs. ibuprofen)	1.28 (0.48, 3.38)	1.12 (0.59, 2.11)	1.12 (0.77, 1.61)	0.68 (0.47, 0.99)*	1.21 (0.74, 1.98)	-	-1.96 (-4.97, 1.05)
Cooke L, *Cochrane Review* 2009, comparison 1	Early asymptomatic indomethacin	0.36 (0.19, 0.68)*	1.32 (0.45, 3.86)	0.91 (0.62, 1.35)	0.41 (0.05, 3.68)	-	-	-5.00 (-17.33, 3.34)
Ohlsson A, *Cochrane Review* 2010, comparison 1	Early asymptomatic ibuprofen	0.27 (0.12, 0.60)*	0.8 (0.34, 1.90)	0.99 (0.88, 1.11)	1.00 (0.64, 1.55)	1.00 (0.47, 2.15)	-	-

*p<0.05
^^ Weighted Mean Differences [WMD] (95% Confidence interval)

5. Trial Objective

5.1. Primary Objective

To determine if selective early treatment of echocardiographically confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth reduces the incidence of death at 36 weeks postmenstrual age or moderate or severe bronchopulmonary dysplasia (BPD) at 36 weeks postmenstrual age.

5.2. Secondary Objectives

To determine if the selective treatment of confirmed large PDAs in extremely preterm babies with ibuprofen within 72 hours of birth results in:

- A reduction in the components of the primary outcome, the duration of ventilation, acute morbidities including necrotising enterocolitis (Bell stage 2 or 3), severe intraventricular haemorrhage (grade 3 or 4), cystic periventricular leukomalacia, retinopathy of prematurity (requiring treatment), failure of PDA closure requiring rescue treatment, side effects of drug treatment, gastrointestinal bleeding and the duration of intensive care (short-term secondary objectives).

- Improved health outcomes at 2 years corrected age including survival without moderate or severe neurodevelopmental disability (long-term primary objective) and survival without respiratory morbidity (long-term secondary objective).

An economic evaluation: an economic evaluation will be carried out from the perspective of the health service. It will take the form of a cost-effectiveness analysis presented in terms of cost per major outcome averted (MOA). The major outcomes are those of the primary outcome, namely death and moderate or severe BPD at 36 weeks. Additional analyses will take place on a range of secondary outcomes and on neurodevelopmental outcomes at 2 years. The incremental cost estimate for statistically significant differences in the pre-specified outcomes in primary and subgroup analyses would be computed.

6. Trial Design

6.1. Summary

This is a multicentre, masked, randomised, placebo-controlled parallel group trial to determine if the treatment of a large PDA with ibuprofen in extremely preterm babies (23^{+0} to 28^{+6} weeks of gestation) improves short and long term health and economic outcomes. The main trial will be preceded by an internal pilot phase which will be used to assess the suitability of trial procedures and likelihood of recruitment targets being achieved.

The entire trial is anticipated to take 82 months to complete and aims to recruit a total of approximately 730 extremely preterm babies.

6.2. Inclusion Criteria

Babies will be considered eligible for inclusion into the trial if they are:

- Born at 23^{+0} to 28^{+6} weeks of gestation
- Less than 72 hours old
- Confirmed by echocardiography as having a large PDA which
  - is at least 1.5 mm in diameter (determined by gain optimised colour Doppler)

  and
  - has unrestrictive pulsatile left to right flow (ratio of flow velocity in PDA Maximum (V_{max}) to Minimum (V_{min}) > 2:1)

In addition:

- The responsible clinician is uncertain about whether the baby might benefit from treatment to close the PDA
- Written informed consent has been obtained from the parent(s)

6.3. Exclusion Criteria

Babies will be excluded from participation in the trial if they have:

- No realistic prospect of survival
- Severe congenital anomaly
- Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen
- Other conditions that would contraindicate the use of ibuprofen (clinically significantly intracranial or gastrointestinal haemorrhage, coagulopathy, thrombocytopenia (platelet count <50,000), renal failure, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC))
- Indomethacin, ibuprofen, or paracetamol administration after birth

6.4. Setting

The trial will be conducted in 25 level 3 neonatal units across the UK (4 units will be involved in the internal pilot phase).

Only units that are in equipoise in the way that they manage PDA, are able and agree to perform echocardiograms within 72 hours of birth to confirm the presence of a large PDA and are part of a Local Clinical Research Network (LCRN) will be selected.

6.5. Primary Outcome

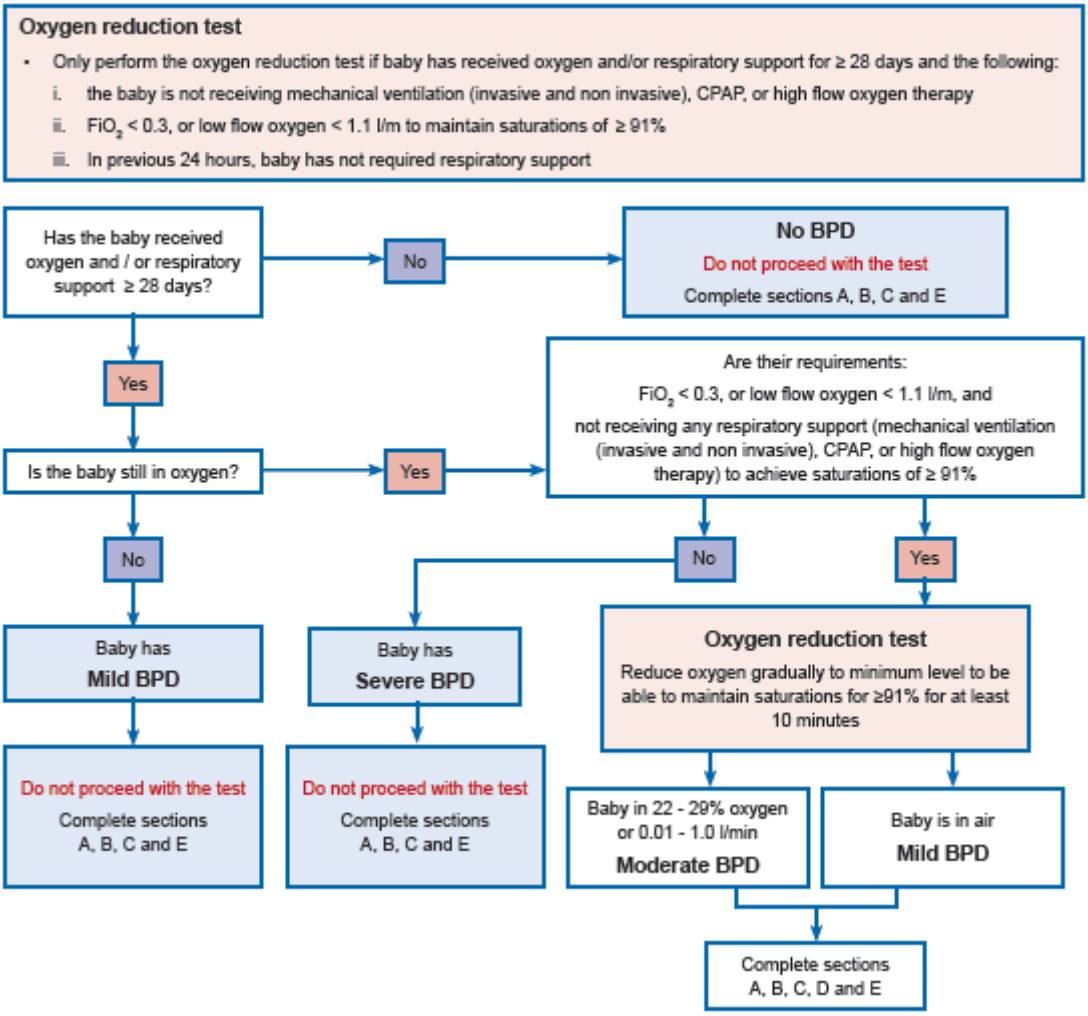
The primary outcome is defined as a composite outcome of death at 36 weeks postmenstrual age, or moderate or severe BPD at 36 weeks postmenstrual age.

TABLE: Severity-Based Diagnostic Criteria for BPD

Time point of assessment:	36 weeks PMA
Therapy with oxygen > 21% and/or respiratory support for ≥ 28 days and the following:	
Mild BPD;	Baby is breathing room air
Moderate BPD;	Baby is in 22 - 29% oxygen, or 0.01 – 1.0 l/min
Severe BPD;	FiO_2 ≥ 0.3, or low flow oxygen ≥ 1.1 l/min, or the baby is receiving any respiratory support (ventilation, CPAP, or high flow oxygen therapy) to achieve saturations of ≥ 91%

The need for oxygen is subjective and hence oxygen dependency will be confirmed using an 'oxygen reduction test'. This is based on the threshold at which the baby is able to maintain oxygen saturations ≥ 91% whilst breathing in air or at a given minimum FiO_2. Babies unable to achieve this will be considered to be oxygen dependent. This test will only apply to those babies whose oxygen requirements are < 0.3, or low flow oxygen < 1.1 l/min, and who have not received any additional respiratory support in the previous 24 hours. Babies outside of this will not be tested, but their oxygen requirements will be captured on the relevant data collection form.

6.5.1. Oxygen Reduction Test



6.6. Secondary Outcomes

Secondary outcomes are divided into short and long term outcomes.

Short term outcomes

- Death at 36 weeks postmenstrual age
- Moderate or severe BPD at 36 weeks postmenstrual age
- Severity of BPD at 36 weeks postmenstrual age (see table in Section 6.5)

Incidence or duration of the following up to discharge:

- Severe intraventricular haemorrhage (IVH) (grade 3/4 with ventricular dilation or intraparenchymal bleeding)
- Cystic periventricular leukomalacia (PVL)
- Retinopathy of prematurity (ROP) requiring treatment
- Significant pulmonary haemorrhage (fresh blood in ET tube with increase in respiratory support)
- Pulmonary hypertension requiring treatment with pulmonary vasodilator

- NEC definitive and/or complicated (Bell stage II and above) confirmed by radiology and / or histopathology
- NEC requiring surgery
- Gastrointestinal bleeding within 7 days of the first dose of trial drug administration
- Spontaneous intestinal perforation
- Closed or non-significant PDA (<1.5 mm) at 3 weeks of age, confirmed by ECHO (or hospital discharge from recruiting centre, if discharged sooner)
- PDA $\geq$ 1.5 mm at 3 weeks, not treated medically or by surgical closure
- Medical rescue treatment of a symptomatic PDA with a COX inhibitor
- Rescue treatment of a symptomatic PDA by surgical treatment
- Administration and duration of inotropic support
- Total duration of respiratory support
    a) Invasive ventilation through an endotracheal tube
    b) Non-invasive support through nasal CPAP, nasal ventilation, or high flow oxygen therapy
- Discharge home on oxygen
- Duration of initial hospitalisation (birth to discharge home)
- Postnatal steroid use for chronic lung disease
- Tolerance of ibuprofen treatment within the safety reporting range described in the protocol (Section 9)

Long Term Outcomes

Secondary long term clinical outcomes assessed at 2 years of age corrected for prematurity:

- Survival
- Survival without moderate or severe neurodevelopmental disability
- Individual components of survival without moderate or severe neurodevelopmental disability (in the four domains of motor, cognitive, hearing and visual function). Cognitive disability will be assessed by determining the Parent Report Composite score obtained through the Parent Report of Cognitive Abilities-Revised (PARCA-R) assessment. The PARCA-R assessment will be adapted to include questions to assess hearing and visual function. Motor function will be assessed using the Gross Motor Function Classification System.
- Respiratory morbidity. Respiratory morbidity will be assessed by the need for oxygen or respiratory support; presence of persistent cough and/or wheeze; need for regular treatment for respiratory illness; unscheduled attendances at hospital/GP; number of re-hospitalisation episodes and duration.

A cost-effectiveness analysis will be conducted of deaths and BPD events avoided and national health services used up to 2 years of age corrected for prematurity.

6.7. Process Outcomes

Process Outcomes will be the following;

- Number of doses of trial medication received
- Adherence to protocol (e.g. protocol violations, incidence of non-symptomatic rescue treatment etc.)
- Study withdrawals

7. Trial Procedures

7.1. Trial Assessments

Procedure	Baby Hospitalisation						Infant 2 Years Corrected Age[6,7,8]
	Screening[1]	Trial Entry and Treatment (days 1–3)	Up to 7 days after trial medication	3 weeks of Age	36 weeks PMA	Discharge	
Demography[10]		✓				✓	✓
Echocardiogram/Colour Doppler[9]	✓			✓			
Confirmation of Eligibility	✓						
Consent		✓					
Randomisation[2]		✓					
Ibuprofen/Placebo Dosing[3]		✓					
IVH / PVL ultrasound scans			✓		✓		
NEC						✓	
Oxygen Reduction Test					✓		
SAEs[4]		✓	✓				
Concomitant Medication[5]	✓	✓		✓	✓	✓	✓
PARCA-R Questionnaire Assessment[6]							✓
Visual Assessment[6]							✓
Hearing Assessment[6]							✓
Motor Assessment[7]							✓
Respiratory Assessment[8]							✓

[1] Screening assessments to be completed sufficiently in advance to enable randomisation and dosing within 72 hours of birth.

[2] Randomisation to be completed sufficiently in advance to enable dosing within 72 hours of birth.

[3] Initial trial drug administrations to be given soon after randomisation and within 72 hours of birth. Subsequent doses to be administered 24 hours after the initial dose.

[4] Only adverse events which are serious will be recorded from first dose until 7 days after trial medication. Only unforeseeable SAEs will be reported.

[5] Concomitant medications to be recorded only in relation to unforeseeable SAEs. In the event of an

unforeseeable SAE all concomitant medication, including medication given to the baby's mother, 7 days prior to the onset of the event to the time of its resolution must be recorded on the SAE form.

[6] Cognitive, visual and hearing function will be assessed using the PARCA-R questionnaire, expanded to include questions to assess visual and hearing function.

[7] Motor function will be assessed using the Gross Motor Function Classification System (GMFCS).

[8] Respiratory assessments will be performed using a separate validated questionnaire. There will be no requirement for the infants to be assessed for respiratory and / or other neurodevelopmental functions by medically qualified personnel.

[9] An echocardiogram scan will be performed when the baby reaches 3 weeks of age or at hospital discharge if discharged earlier.

[10] Demography and medications will be assessed through the PARCA-R and other questionnaires.

7.2. Structure and Duration of the Trial

The total duration of recruitment into this trial will consist of an internal pilot phase (9 month recruitment period) and main trial (36 month recruitment period). The aim is to recruit approximately 730 babies from participating neonatal units across the UK in about 45 months (internal pilot and main trial).

For the main trial, the recruitment period is based on an approximate yearly admittance of 2,000 babies born between 23 and 28 weeks of gestation to the 25 participating level 3 neonatal units and the assumption that about 46% of these babies will have a large PDA [Stoll et al, 2010]. This would result in approximately 900 babies being eligible for inclusion in this trial. Assuming a conservative uptake rate of 20−30% this would equate to around 250 babies being enrolled per year (1 per unit per month).

The trial will consist of an internal pilot phase, run over a period of 13 months (including a 4 month trial set up period), in four level 3 neonatal units to test whether the current trial design and associated procedures will allow overall recruitment targets to be achieved. Projections suggest that around 30 babies should be recruited in that time. Data collected from the internal pilot phase of the trial will be included in the final analysis.

The decision to progress to the main trial using the current design will be made in consultation with the Trial Steering Committee (TSC) and funder. Stop/go criteria upon which a decision will be made will be established prior to the start of the internal pilot phase. Should a decision be made not to progress to the main phase, a report on the internal pilot phase will be submitted for publication according to the publication policy.

All enrolled babies will be followed up at 2 years of age corrected for prematurity. Thus the duration of trial participation will be up to 28 months (2 years corrected age). Where we have been unable to contact families within this timeframe we will attempt to collect information about infants in the trial until the end of the funding. Further longer term follow-up at primary school age may be considered but will require separate funding. This may be undertaken as an amendment to this trial or as a separate application depending on the circumstances at the time.

7.3. Initial Eligibility Assessment

Extremely preterm babies potentially suitable for the trial will be identified by the healthcare team within the neonatal unit. Babies however will only be considered eligible for enrolment into the trial and their parent(s) approached for consent after they have undergone an echocardiogram and Doppler assessment and have been confirmed to have a large PDA.

The initial echocardiogram and Doppler assessment will incorporate:

- Size of the PDA and flow pattern according to standard trial methodology
- Size of the PDA will be determined at the site of maximum constriction (minimum diameter) using gain optimisation typically at the pulmonary end by determining the average of 3 separate clips
- If the size of the PDA is at least 1.5 mm, flow pattern will be determined by placing the pulse gate in the PDA while adjusting the velocity scale to its highest setting. If the shunt direction is >1/3 duration of a cycle being right to left, then a rescan will be attempted after a few hours.

If the echocardiogram findings raise concerns about possibility or diagnosis of congenital heart disease, a referral will be made to a paediatric cardiologist as per clinician discretion.

7.4. Informed Consent

Written informed consent will be sought from parent(s) of potentially eligible babies only after the baby has been confirmed to have a large PDA and the baby's parent(s) have been given a full verbal and written (via the Parent Information Leaflet (PIL)) explanation of the trial. Parent(s) who do not speak English will only be approached if an adult interpreter is available. Relatives may not interpret.

Written informed parental consent will be obtained by means of a dated parental signature and the signature of the person who obtained informed consent; this will be the Principal Investigator (PI) or appropriately qualified healthcare professional who has been delegated authority. A copy of the signed informed consent form (ICF) will be given to the parent(s). Further copies with be retained in the baby's medical notes and by the PI. The original signed consent form will be sent to the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU).

7.5. Randomisation

Treatment allocation of ibuprofen or placebo will be in a ratio of 1:1 and masked such that the allocation will not be known by clinicians, the baby's family or the trial outcome assessors.

Randomisation will be managed via a secure web-based randomisation facility hosted by the NPEU CTU with telephone back-up available at all times (24/7, 365 days a year). The randomisation program will use a minimisation algorithm to ensure balance between the groups with respect to the size of the PDA, gestational age at birth, age at randomisation, sex, trial site, multiple births, mode of respiratory support at randomisation (1) invasive ventilation (by an endotracheal tube), or (2) non-invasive respiratory support (nasal CPAP, nasal ventilation, or high flow oxygen therapy - humidified high flow nasal cannula), or (3) receiving no mechanical or pressure support (in room air or low flow or ambient oxygen) and receiving inotropes or not at the time of randomisation. Babies of multiple births will be randomised individually.

The Senior Trials Programmer at the NPEU CTU will write the randomisation program and hold the treatment allocation codes. If necessary, the code may be broken for a single baby at the request of the site PI or clinician in charge of the baby. See Section 8.6 for the procedure for unmasking treatment allocation.

7.6. Echocardiograms

Echocardiograms are performed as part of the normal care of preterm babies. However, clinicians will be required to perform an echocardiogram within 72 hours of birth, at 3 weeks of age or at discharge from the neonatal unit if discharged before this time.

Echocardiogram scans will be reviewed by a qualified clinician, who is not involved in recruiting for the trial, to assess consistency between clinicians. All babies recruited to the internal pilot phase and a randomly selected sample from the main trial, equating to 10% of echocardiogram scans used to confirm trial eligibility, will be reviewed. Principal Investigators will be informed of the review findings.

Training will be provided during the trial to minimise any variations in practice. Any difference in measurements between the site investigator and reviewer will be documented to aid with on-going training. Details of both the echocardiogram procedures to be followed and the process for submitting scans for independent review will be described in a separate handbook.

7.7. Concomitant Medications

Concomitant medication given to a baby will be recorded in the event that an unforeseeable serious adverse event is reported for that baby. If such an event is reported, all concomitant medication given 7 days prior to onset of the event, including medication given to the baby's mother if 7 days is prior to the birth of the baby, up to its resolution will be detailed on the SAE form provided for the trial.

7.8. Permitted and Non-Permitted Medications

All prescribed medications deemed necessary to provide adequate supportive care to the baby, are permitted at any stage during the trial period. However, open treatment with indomethacin or ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided unless the criteria for rescue treatment (defined in Section 8.4) are met.

As a NSAID, ibuprofen may interact with the following medicinal products:

- Diuretics – ibuprofen may reduce the effect of diuretics; diuretics can increase the risk of nephrotoxicity of NSAIDs in dehydrated patients
- Anticoagulants – ibuprofen may increase the effect of anticoagulants and enhance the risk of bleeding
- Corticosteroids – ibuprofen may increase the risk of gastrointestinal bleeding
- Nitric oxide – since ibuprofen also inhibits platelet function, combining the drugs may in theory increase the risk of bleeding
- NSAIDs – the concomitant use of more than one NSAID should be avoided because of the increased risk of adverse reactions

The concomitant administration of other medication is not restricted but should be closely monitored for an interaction by the treating clinician.

7.8.1. Supportive Care of Enrolled Babies

The management of babies including ventilator management and fluid therapy during intensive or high dependency care will be guided by the European Consensus Guidelines for Management of Respiratory Distress Syndrome (RDS) in preterm babies. An effort will be made to minimise the differences in treatment practices between sites through training on the guidelines.

7.9. Stopping Trial Interventions

The intervention may have to be (temporarily) stopped if the baby develops any adverse effects necessitating stoppage. For example, if anuria, marked oliguria (<0.6 ml/kg/hr), or clinically significant bleeding is evident at the scheduled time of the second or third dose, no additional dosage should be given until laboratory results indicate that renal function has returned to normal, or bleeding has stopped. In the event of GI perforation discontinue trial medication.

At all stages it will be made clear to the parent(s) that they remain free to withdraw their baby from the trial at any time without the need to provide any reason or explanation. Parent(s) will be made aware that a decision to withdraw their baby will have no impact on any aspect of their baby's continuing care. If parent(s) choose to withdraw their baby from trial participation, permission will be sought to complete data collection and use data up to the point of withdrawal from the trial.

A baby may also be withdrawn from the trial, if deemed by the Principal Investigator to be in their best interests.

7.10. End of Trial

The end of trial will be defined as the last infant's assessment at 2 years of age corrected for prematurity. An End of Trial Declaration will be made to the Medicines and Healthcare products Regulatory Agency (MHRA) and approving Research Ethics Committee (REC) within 3 months of this date.

7.11. Early Trial Cessation

A decision may be made by the Trial Steering Committee (TSC) to stop the trial early following a recommendation from the Data Monitoring Committee (DMC), on review of interim trial data, or evidence from other relevant studies becoming available. Guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

7.12. Remuneration

No financial or material incentive or other form of compensation will be given to babies or their parent(s) as a result of taking part in this trial.

8. Investigational Medicinal Product (IMP)

8.1. Dosing and Administration

Ibuprofen will be supplied as a clear sterile preservative-free solution at a concentration of 10 mg/ml in vials. Cartons containing three single use vials will be provided. Each carton will be labelled with a unique code and in compliance with the guidance given in Annexe 13 of the European Commission's guidelines for Good Manufacturing Practice.

An initial loading dose of 10 mg/kg (1 ml/kg) of ibuprofen will be administered, followed by two 5 mg/kg (0.5 ml/kg) doses at 24 and 48 hours after the initial dose. Doses are to be calculated on the birth weight of the baby and diluted to appropriate volume with dextrose or saline. Each dose is to be given as a short intravenous infusion over 15 minutes. All 3 doses will be given unless there are adverse effects necessitating stoppage, as referenced in Section 7.9. Placebo will be supplied as a clear sterile solution of 0.9% saline solution for injection. Cartons identical to those for ibuprofen, each containing three identical single use vials will be provided. Volume of IMP to be withdrawn from the vial will be calculated following the calculations for ibuprofen dosing and then diluted with dextrose or normal saline for administration.

Following randomisation, first dose should be administered soon after randomisation and within 72 hours of birth. The recommended storage will be in line with the Full Prescribing Information and once the vial is opened the drug must be used immediately.

8.2. Distribution

Sufficient supplies of IMP will be provided to each site. Distribution and use of IMP will be tracked by the staff at the NPEU, using a 'pack management system' and additional supplies provided as and when needed.

8.3. Accountability

Trial drug packs will be dispensed by pharmacy and stocked on the neonatal units. The dispensing of the trial drug from pharmacy will require a completed prescription form. Detailed accountability records will be maintained to document which pack of medication is dispensed to which baby. Site staff will be required to write the baby's trial number and initials on the trial pack allocated. Part used packs will be kept separate from unused packs.

Pharmacy will maintain an overall inventory of stock received and dispensed.

8.4. Rescue Treatment

If the clinical condition of a baby warrants intervention, rescue treatment can be given to close the PDA (medical or surgical). The following criteria however have been devised to limit and rationalise the use of rescue treatment but it is recognised that clinicians may need

to override this guidance in the best interests of the baby. Clinical responsibility for the care of the baby will remain fully with the neonatal clinical team irrespective of the trial.

Rescue treatment (both medical and surgical) is permitted within the protocol if the following minimum criteria are met and other medical management strategies have been tried. Surgical treatment however should only be considered if the PDA remains persistently large after one course of treatment with a COX inhibitor or in circumstances where medical treatment may be contraindicated or time does not permit medical rescue treatment first.

1. Inability to wean on ventilator (ventilated for at least 7 days continuously) and inability to wean oxygen, or
2. Persistent hypotension/pulmonary haemorrhage/signs of cardiac failure

AND

3. Echocardiographic findings of a large PDA (PDA ≥ 2.0 mm with pulsatile flow) AND hyperdynamic circulation or ductal steal (refer to Baby-OSCAR ECHO workbook).

All rescue treatment will be administered in an open fashion.

A persistent open PDA requiring open label treatment (medical or surgical) should be reported to the trial co-ordinating centre using Form 5: Rescue Medication Form.

8.5. Masking of Trial Medication

Ibuprofen and placebo will be indistinguishable from each other. To maintain masking, each baby will be issued a unique allocation number that will correspond to a carton number.

8.6. Procedure for Unmasking

In the event of an emergency, a baby's treatment allocation may be unmasked by contacting the NPEU CTU during working hours, or calling an out of hours help line managed by a company called Message Direct who will contact appropriate people. The contact details for both the NPEU CTU and Message Direct are as follows:

9:00 am to 5.00 pm	NPEU CTU:	01865 617 965
5.00 pm to 9.00 am and weekends	Message Direct:	0800 138 5451

Details of contact numbers will also be filed in the Investigator Site File.

Details of the person requesting unmasking and the reason for the request will be recorded.

Wherever possible, the unmasking of a baby's treatment allocation should be discussed with

the Chief Investigator or delegate in advance.

9. Safety Reporting

9.1. Definitions

9.1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a participant administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial medication, whether or not considered related to the trial medication.

9.1.2. Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose. The phrase “response to a medicinal product” means that a causal relationship between trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

9.1.3. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

The term ‘severe’ is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance. This is not the same as ‘serious’, which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning.

The term ‘life-threatening’ in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event is serious in other situations.

9.1.4. Foreseeable Serious Adverse Events

Foreseeable SAEs are those events which are foreseen in the patient population or as a result of the routine care/treatment of a patient.

The following serious adverse events are a foreseeable occurrence in this population of preterm babies and as such do not require reporting as SAEs:

- Death (unless unforeseeable in this population)
- Respiratory failure
- Pulmonary haemorrhage
- Necrotising enterocolitis
- Clinically significant intracranial abnormality on cranial ultrasound scan – intracranial haemorrhage or white matter injury
- Retinopathy of prematurity
- Hypotension
- Hyperbilirubinemia necessitating exchange transfusion
- Pulmonary hypertension requiring treatment with pulmonary vasodilator
- Spontaneous intestinal perforation
- Impaired renal function (urine output <0.5 mL/kg/hour, and or serum creatinine > 100 µmol/L)
- Anaemia requiring transfusion
- Hypoglycaemia
- Hyperglycaemia
- Haemothorax
- Culture proven sepsis
- Coagulopathy requiring treatment
- Sepsis / ventilator associated pneumonia
- Pneumothorax or air leaks
- Seizures not related to an intracranial event
- Gastrointestinal haemorrhage

9.1.5. Unforeseeable Serious Adverse Events

An unforeseeable SAE is any event that meets the definition of a SAE and is not detailed in the list above as foreseeable. These events should be reported on the trial SAE form provided following the procedures detailed in Section 9.2.1.

9.1.6. Serious Adverse Reaction (SAR)

A serious adverse reaction is a SAE which is considered to have been caused by the administration of trial medication. For a SAE to be considered as a reaction there must be a

reasonable probability that it was related to the administration of IMP.

9.1.7. Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is a SAR, the nature or severity of which is not consistent with the known safety profile of the trial medication (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics for an approved product). The Reference Safety Information for the L-lysine salt of ibuprofen is contained within the Full Prescribing Information which will be used to assess the expectedness of adverse events.

9.1.8. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Unrelated; where an event is not considered to be related to the IMP;

Possibly; although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible;

Probably; the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP;

Definitely; the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

All SAEs as discussed in Section 9.2.1 labelled possibly, probably, or definitely will be considered as related to the IMP.

9.1.9. Assessment of Safety

During the course of the trial, safety data will be reviewed by the Data Monitoring Committee (DMC). This will include safety data for SAEs as stated in Section 9.2.1 as well as Section 9.1.4 and 9.1.5. The DMC will, if appropriate, make recommendations regarding continuance of the trial or modification of the trial protocol. The TSC will have ultimate responsibility for deciding whether the trial should be stopped on safety grounds.

9.2. Reporting Procedures

9.2.1. AE/SAE Reporting

Causality of adverse events reported in the preterm newborn is difficult to assess since they may be related to the haemodynamic consequences of the patent ductus arteriosus as well as to

direct effects of ibuprofen. In addition to this, high incidences of adverse events are foreseeable due to the nature of the patient population and the routine care / treatment. Consequently, only those adverse events identified as serious will be recorded for the trial.

Safety reporting as described in this section for the baby will be monitored from first dose until 7 days after trial medication. Unforeseeable Serious Adverse Events will be reported to the NPEU CTU within 24 hours of staff at the site becoming aware of the event. Details will be recorded on a SAE form (filed in the Investigator Site File) and the form faxed or emailed back to the NPEU CTU. If this is not possible, the unforeseeable SAE may be reported by telephone and the SAE form completed by staff at the NPEU CTU. Follow-up information should be reported on a new SAE form and this forwarded to the NPEU CTU by fax or email.

NPEU will review the report, request any additional information and ensure it is assessed by the CI or his delegate within the reporting timeframe. It will also be reviewed at the next DMC meeting. The CI will inform all Principal Investigators of relevant information that could adversely affect the safety of the participants.

9.2.2. SUSAR Reporting

SUSARs will be reported to the MHRA and the approving Research Ethics Committee (REC) within 7 days if the event resulted in death or was life-threatening and within 15 days for all other SUSARs. In addition, a copy of the SAE form corresponding to the event will be forwarded to the Chair of the DMC. The Chair will also be provided with details of the baby's treatment allocation if requested.

9.2.3. Development Safety Update Report (DSUR)

In addition to the expedited reporting detailed above, the CI will submit a Development Safety Update Report (DSUR) once a year throughout the duration of the trial to the MHRA and REC.

10. Statistics and Analysis

10.1. Sample Size

Evidence from the TIPP trial suggests that the risk of death or BPD in extremely low birth weight babies at 36 weeks postmenstrual age allocated placebo is 52% (95% CI 48% to 56%) [Schmidt et al, 2001]. However this trial investigated the effect of prophylactic treatment and included all babies weighing 500−999g. More recent information using data derived from the latest report of Neonatal Survey Database from the Trent region (2010) provides an approximate rate of death or BPD at 36 weeks postmenstrual age of 53% for all babies admitted to the neonatal unit. These babies would have been treated according to

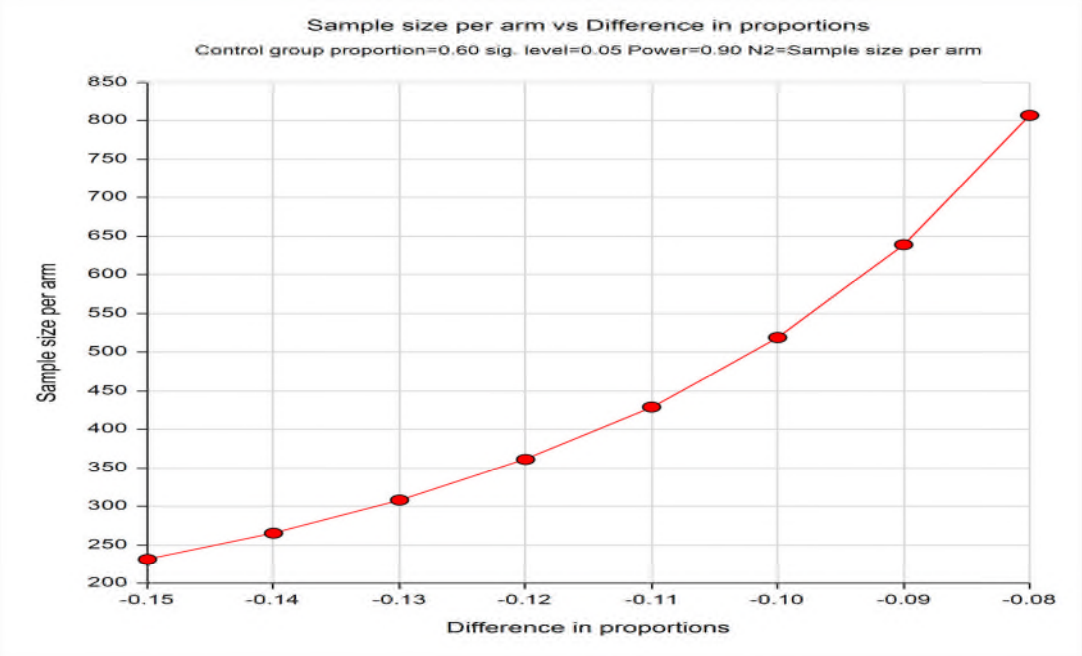
clinical judgement and therefore a proportion of them would have been treated with ibuprofen. Given the risk of death or BPD in babies with a large PDA is inherently higher, it is estimated that the risk in this group is 60%.

Su et al (2008) compared ibuprofen to indomethacin in babies ≤ 28 weeks of gestation having a PDA who were less than 24 hours old. The combined outcome of death within 30 days or BPD at 36 weeks postmenstrual age was observed to be 42% (95% CI 29% to 55%).

It is therefore expected, given that babies will be enrolled up to 72 hours after birth, that the treatment group incidence of death/BPD at 36 weeks will be approximately 48% in the intervention arm. This would imply an absolute risk reduction of 12% (60% to 48%) in the primary outcome of the trial for babies randomised to treatment compared to placebo, which is considered a clinically important difference.

Some babies will require rescue treatment in either the treatment or placebo arm. As rescue treatment should be limited to symptomatic babies meeting only defined criteria, it is considered to have minimal or no effect on the primary outcome. Thus adjustment of the sample size for rescue treatment is not considered necessary.

The following graph depicts a sample size curve for the primary outcome of the trial of death or BPD at 36 weeks postmenstrual age, assuming 90% power, a two-sided 5% significance level and a 60% control group event rate for the primary outcome.



This table summarises this information and allows for 1% loss to follow-up in the primary outcome. Minimal loss to follow-up is expected for the primary outcome since it is a short term outcome and recorded whilst the baby is in hospital.

Control group event rate	Active Rx group event rate	Absolute risk reduction	Relative risk reduction	Approximate total sample size required
60%	47%	13%	22%	620
60%	**48%**	**12%**	**20%**	**730**
60%	49%	11%	18%	870

Thus a sample size of approximately 730 babies in total (365 per arm) would be required to detect an absolute risk reduction of 12% (power 90%, 2-sided significance level of 5%) from a control group event rate of 60% to a treatment group event rate of 48%, assuming 1% lost to follow-up.

Regarding outcomes at 2 years corrected age, assuming the risk of a child dying before two years of age is 10%, questionnaires will be sent out to around 660 parents of surviving children. Assuming an attrition rate of 20% reduces the sample size to around 530. The proportion of infants surviving to 2 years without moderate or severe neurodevelopmental disability in the control group is expected to be 55% [Mangham et al, 2009]. With outcome data available on a total sample size of around 600 (including deaths) the trial will have an 80% power to detect an increase in survival without moderate or severe neurodevelopmental disability of 11% from 55% to 66% and 90% to detect an increase of 13% from 55% to 68%.

10.2. Assessment of Outcomes

Short term outcome data will consist of routine clinical and laboratory assessments. The timing and methods for assessing and determining the short outcomes are consistent with those routinely performed for babies in intensive/high dependency care.

Long term outcomes will be assessed using validated parent report questionnaires. Standardised measures (Gross Motor Function Classification System and PARCA-R) and additional questionnaire items designed to elicit key information regarding visual and hearing impairment, respiratory morbidity and health economic outcomes will be combined into a single trial specific questionnaire, which will be posted to parents one week prior to the date on which the child would have turned 2 years old if they had been born at term (40 weeks). The Health and Social Care Information Centre (HSCIC) will be used to alert the Trial Co-ordinating Centre of deaths prior to follow-up.

To estimate the costs associated with the echocardiography/Doppler screening within 72 hours of birth in preterm babies, the following will be monitored;

- Staff resource used to carry out echocardiogram/Doppler screening within 72 hours compared with current practice
- The time, resource and unit costs associated with medication or tests and procedures as a result of earlier screening

- Requirement for neonatal medication
- Duration of stay in neonatal intensive care and inpatient days
- Admissions after discharge

Unit costs will be given to each resource item to determine an overall cost per baby. Primary cost data for many of the resources will be collected from participating hospital sites. Where possible other costs data such as cost of a clinician's time to perform an assessment will be collected from hospital finance departments. Most cost data is already available in published sources. For example, a study to investigate the costs of different levels of neonatal intensive care has already been carried out and other cost studies with relevant costs and costs associated with preterm delivery are available to supplement these [Petrou et al, 2003; Roberts et al, 2012].

10.3. Statistical Analysis

10.3.1. Primary Analysis Population

Babies will be analysed in the groups to which they are randomly assigned, comparing the outcome of all babies allocated to ibuprofen with all those allocated to placebo, regardless of deviation from the protocol or treatment received (referred to as the Intention to Treat (ITT) population).

10.3.2. Statistical Methods

Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables. All comparative analyses will be performed adjusting for minimisation factors at randomisation [Brennen CK and Morris TP, 2013]. The adjusted analysis will also account for the correlation of outcomes among babies from multiple births included in the trial. Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios plus confidence intervals. If the model does not converge, then centre will be removed as a stratification factor in the first instance. If the model is still unstable then log Poisson regression models with robust variance estimation will be used [Zou G, 2014]. Continuous outcomes will be analysed using linear regression models and results will be presented as adjusted differences in means (plus confidence intervals). Analysis of time to event outcomes will use survival analysis techniques.

Process outcomes including the number of doses received, adherence to the protocol and study withdrawals will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables.

10.3.3. Pre-specified Subgroup Analysis

Pre-specified subgroup analysis will use the statistical test of interaction (or test for trend) and where appropriate, results will be presented as risk ratios with confidence intervals. Pre-specified subgroups will be based on gestational age, size of the PDA and mode of respiratory support.

10.3.4. Level of Statistical Significance

95% confidence intervals will be used for all primary outcome comparisons including subgroup analysis; to take account of the multiplicity of secondary outcomes, 99% confidence intervals will be presented.

10.3.5. Dealing with Missing Data

Missing data as a result of babies being lost to follow-up is expected to be minimal for short term outcomes. For 2 year outcomes, all reasonable measures will be taken to minimise loss to follow-up which is expected to be no more than 20% (excluding deaths after randomisation). Babies for whom no 2 year follow-up data are received will be compared to babies with 2 year data on demographic and clinical characteristics as well as short term outcomes, to assess generalisability. As there is expected to be a link between severity of disability and loss to follow-up, imputation techniques will not provide any meaningful information.

10.4. Economic Analysis

Health economic outcomes will take the form of a cost-effectiveness analysis of deaths and any moderate or severe BPD at 36 weeks postmenstrual age avoided, as well as analysis of the cost implications of secondary outcomes. Analysis will be from the perspective of the NHS so only direct NHS costs will be collected.

To determine economic outcomes, a within trial analysis will be conducted but a model based analysis beyond the end point of the trial will also be considered.

The within trial analysis will be based on two clinical endpoints. The first within trial analysis will be based on the composite clinical outcome of death avoided and/or case of moderate or severe BPD eliminated at 36 weeks postmenstrual age (this outcome can also be interpreted for the economic analysis as survival at 36 weeks postmenstrual age without severe or moderate BPD). The result of the economic evaluation will be reported as the additional cost per additional case of death or severe or moderate BPD avoided at 36 weeks postmenstrual age compared to conventional treatment. This analysis will only use data collected up to the assessment at 36 weeks postmenstrual date or discharge, whichever is later.

The second within trial analysis will be based on the clinical endpoint assessed at two years of age, of survival without severe or moderate neurodevelopmental disability. The analysis will include all cost and resource use data up to the infant reaching 2 years of age, based on data from the parent report and neurodevelopment assessment. It may be deemed appropriate to model beyond the end point of the trial if sufficient data are available. However the limitations of modelling beyond this point will be emphasised.

A bootstrapping approach to calculate the confidence intervals around differences in costs will be used to account for the skew inherent in most cost data. As a first step the analysis will take the form of a cost-consequences analysis, reporting data in a disaggregated manner on the cost and important consequences as determined in the trial. If a situation of dominance exists where, for example, the new intervention is more costly but less effective than the current intervention (dominated by the existing intervention) or conversely less costly but more effective than the existing intervention (the new intervention dominates the existing intervention), then the cost consequence analysis would establish that no further analysis is required. However, it is more likely that any additional benefit will be accompanied by additional costs and so a full incremental economic evaluation in terms of a cost effectiveness analysis will be carried out and the results presented in terms of additional cost per additional unit of effect.

10.5. Measures to Minimise Bias

The allocation of trial treatment is randomly assigned and concealed using a central secure web-based system and trials medications are masked such that medical and nursing staff, as well as outcome assessors and parents will be unaware of the trial medication administered. No crossover of groups is allowed; however rescue treatment will be permitted if certain pre-defined criteria are met.

11. Source Data/Documents

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from the NPEU CTU, the Sponsor, the MHRA and the host organisation to permit trial-related monitoring, audits and inspections.

12. Quality Control and Assurance

12.1. Risk Assessment

The NPEU CTU has performed a risk assessment of the trial prior to commencement that will be reviewed at regular intervals during the course of the trial.

12.2. National Registration Systems

The trial will be registered on at least one global trial register.

An International Standard Randomised Controlled Trial Number (ISRCTN) has also been sought.

All babies will be registered on the HSCIC register.

12.3. Site Initiation and Training

Initiation visits at each participating neonatal unit will be performed by the Chief Investigator or his delegate and a Local Research Nurse (LRN) once all appropriate approvals are in place and IMP has been shipped to the site to train site staff on trial procedures.

The LRN will ensure adherence to the protocol and deal with any specific site issues. They will also be responsible for organising trial days to ensure that all appropriate site staff are kept fully appraised of issues such as recruitment status, informed consent, data collection, follow-up and changing regulations.

12.4. Site Monitoring and Auditing

The LRN, along with the PI, will facilitate the day to day smooth running of the trial at the site. They will encourage recruitment, provide staff education and training, and monitor data completeness and quality.

The LRN will submit written site visit reports to an appropriate representative of the Project Management Group (PMG) based at the NPEU CTU. No routine monitoring will be carried out unless there is cause for concern regarding the conduct of the trial at a site as a result of central monitoring. Similarly, sites will only be audited if there is a reason. This level of monitoring is justified by the level of risk associated with the trial and the use of IMP.

12.5. Blinded Endpoint Review

Given the subjective nature and complexity of diagnosis for the outcomes listed below, a small number of clinicians, as well as an independent radiologist, will review all of the data relating to outcomes listed below for the internal pilot phase and at least 10% for the main trial. The outcomes are:

- Severe intraventricular haemorrhage (IVH) (grade 3/4 with ventricular dilation or intraparenchymal bleeding)
- Cystic periventricular leukomalacia (PVL)
- NEC definitive and/or complicated (Bell stage II and above) confirmed by radiography and / or histopathology.

13. Serious Breach of Good Clinical Practice or the Trial Protocol

The MHRA require that they be informed of all serious breaches in good clinical practice (GCP) or the trial protocol within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as a breach of GCP or the trial protocol which is likely to affect to a significant degree –

- The safety or physical or mental integrity of the patient on the trial or
- The scientific value of the trial

In the event that a serious breach is suspected the Trial Co-ordinating Centre should be contacted as soon as possible. The Trial Co-ordinating Centre will refer the serious breach onto the Sponsor immediately.
The Chief Investigator or their delegate will also notify any protocol violations to the Sponsor and will notify the REC of these in accordance with trial procedures.

14. Ethics

14.1. Declaration of Helsinki

The Investigators will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The trial will only start after gaining approval from the MHRA and a registered REC. Additionally, approval of the appropriate NHS Trust Research and Development Office will be sought for individual trial sites.

Applications will be submitted through the Integrated Research Application System (IRAS).

A copy of the protocol, Parent Information Leaflet and Informed Consent Form, GP letter will be submitted to the MHRA and the REC for approval. The Chief Investigator or their delegate will submit and, where necessary, obtain approval from the MHRA and REC for any substantial amendments. Substantial amendments are defined as those that affect:

- the safety or physical or mental integrity of the participants of the trial;
- the scientific value of the trial;

- the conduct or management of the trial; or
- the quality or safety of any investigational medicinal product used in the trial.

14.4. Participant Confidentiality, Data Handling and Record Keeping

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the trial sponsor. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998). Data collected on the data collection forms (DCFs) will be transferred for storage in an electronic database held by the Trial Co-ordinating Centre in which the participant will be identified only by a trial specific number.

Contact details of the baby's parent(s), as well as the baby's name (if known) and any other identifying details will be stored in a separate database also held at the NPEU CTU. This database will only be linked to the database containing trial data by the baby's trial number.

After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

Electronic files will be stored on a file server that has restricted access. The server is in a secure location and access is restricted to a few named individuals. Access to the building in which the NPEU CTU is situated is via an electronic tag and individual rooms are kept locked when unoccupied. Authorisation to access restricted areas of the NPEU CTU network is as described in the NPEU CTU security policy. Data will be processed on a workstation by authorised staff. The computer workstations access the network via a login name and password which is changed regularly. No data are stored on individual workstations. Back-up of data is done automatically overnight to an offsite storage area. The location of the back-up computer is in a separate department which has electronic tag access. Access to the room in which the back-up machine is located is via a key-pad system.

14.5. Retention of Personal Data

Personal data will be needed to contact parents when their children are 2 years of age, to co-ordinate follow-up, and to disseminate the results of the trial to parent(s). Due to the nature of neonatal research the NPEU policy is to keep personal data for a period of no less than 25 years in order to follow-up on health related issues which may become relevant in the future. At all times personal data will be held securely and will not be used for any other purpose.

14.6. Funding

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is funding the trial.

14.7. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

15. Trial Governance

15.1. Site Research and Development Approval

Individual sites will only commence recruiting participants once they receive approval from NHS Trust Research and Development (R&D) Offices. Applications to R&D offices will be submitted through the NIHR Co-ordinated System for gaining NHS permission.

15.2. Trial Sponsor

The University of Oxford is the nominated Sponsor for the trial.

15.3. Co-ordinating Centre

The trial co-ordinating centre will be at the NPEU CTU, University of Oxford where the Trial Co-ordinator will be based. The NPEU CTU will be responsible for all trial programming, randomisation, data entry, statistical analyses and, in collaboration with the Chief Investigator and the Local Research Nurse(s), manage the day-to-day running of the trial including recruitment of centres and training of staff. The NPEU CTU will also service both the DMC and TSC.

15.4. Project Management Group (PMG)

The trial will be supervised on a day-to-day basis by the Project Management Group. This group reports to the Trial Steering Committee (TSC) which is responsible to the trial sponsor. At each participating centre, a local Principal Investigator will report to the PMG via the staff based at the NPEU CTU.

The core PMG will consist of the CI and NPEU CTU staff including:

- CTU Director
- Senior Trials Manager
- Senior Trials Programmer
- Trial Co-ordinator
- Trial Statistician
- Trial Programmer
- Administrator/Data Manager

The core PMG will meet regularly (at least monthly).

15.5. Co-investigators' Group (CIG)

The CIG will meet at least twice a year. This will comprise all co-applicants and the members of the core PMG.

15.6. Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent chair and at least two other independent members. Committee members will be deemed to be independent if they are not involved in trial recruitment and are not employed by any organisation directly involved in the trial conduct.

Representatives from relevant Patient/Public Involvement groups, the Chief Investigator, other Investigators/co-applicants will be joined by observers from the NPEU CTU. The HTA programme manager will be invited to attend all TSC meetings.

The role of the TSC is to provide the overall supervision of the trial. The TSC should monitor the progress of the trial and conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

15.7. Data Monitoring Committee (DMC)

A DMC, independent of the applicants and of the TSC, will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC and (via the TSC) to the HTA. The committee will periodically review trial progress and outcomes as well as secondary outcomes (e.g. death, severe IVH, etc.). The content and timings of the DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.

16. Publication Policy/Acknowledgement of Contribution

The success of the trial depends on a large number of neonatal nurses, neonatologists, and parent(s). Credit for the trial findings will be given to all who have collaborated and participated in the trial including all local co-ordinators and collaborators, members of the trial committees, the Baby-OSCAR Co-ordinating Centre and trial staff. Authorship at the head of the primary results paper will take the form "[name], [name] and [name] on behalf of the 'The Baby-OSCAR Collaborative Group'". The drafting of the paper will be the responsibility of a writing committee. All contributors to the trial will be listed at the end of the main paper, with their contribution identified.

17. Protocol Signature

17.1. Principal Investigator Signature

By signing this protocol signature page, I agree to:

- Conduct the trial in accordance with the protocol and only make changes in order to protect the safety, rights or welfare of the participants.
- Personally conduct or supervise the trial and ensure that all associates, colleagues and employees assisting in the conduct of the trial are informed about their obligations.
- Ensure requirements with regard to obtaining informed consent are adhered to.
- Report AEs/SAEs that occur during the course of the trial and maintain adequate and accurate records to enable representatives of the Sponsor or regulatory authority to confirm adherence with the protocol.

Principal Investigator's Signature	Date

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